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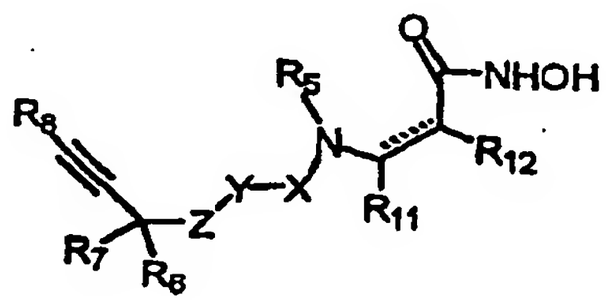


(B)

(57) Abstract

The invention discloses hydroxamide acids of formula (B) which are useful in treating disease conditions mediated by TNF–α, such as rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease and degenerative cartilage loss. In the above formula, the dotted line represents an optional double bond, and $R_5$, $R_6$, $R_7$, $R_8$, $R_{11}$, $R_{12}$, X, Y and Z have the meanings given in the specification.

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# ACETYLENIC β-SULFONAMIDO AND PHOSPHINIC ACID AMIDE HYDROXAMIC ACID TACE INHIBITORS

## FIELD OF INVENTION

This invention relates to acetylenic aryl sulfonamide and phosphinic acid amide hydroxamic acids which act as inhibitors of TNF-α converting enzyme (TACE). The compounds of the present invention are useful in disease conditions mediated by TNF-α, such as rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease and degenerative cartilage loss.

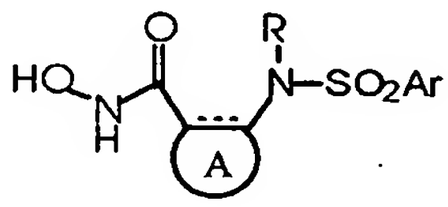
## BACKGROUND OF THE INVENTION

TNF-α converting enzyme (TACE) catalyzes the formation of TNF-α from membrane bound TNF-α precursor protein. TNF-α is a pro-inflammatory cytokine that is believed to have a role in rheumatoid arthritis [Shire, M. G.; Muller, G. W. *Exp. Opin. Ther. Patents* **1998**, *8(5)*, 531; Grossman, J. M.; Brahn, E. *J. Women's Health* **1997**, *6(6)*, 627; Isomaki, P.; Punnonen, J. *Ann. Med.* **1997**, *29*, 499; Camussi, G.; Lupia, E. *Drugs*, **1998**, *55(5)*, 613.] septic shock [Mathison, *et. al. J. Clin. Invest.* **1988**, *81*, 1925; Miethke, *et. al. J. Exp. Med.* **1992**, *175*, 91.], graft rejection [Piguet, P. F.; Grau, G. E.; *et. al. J. Exp. Med.* **1987**, *166*, 1280.], cachexia [Beutler, B.; Cerami, A. *Ann. Rev. Biochem.* **1988**, *57*, 505.], anorexia, inflammation [Ksontini, R,; MacKay, S. L. D.; Moldawer, L. L. *Arch. Surg.* **1998**, *133*, 558.], congestive heart failure [Packer, M. *Circulation*, **1995**, *92(6)*, 1379; Ferrari, R.; Bachetti, T.; et. al. *Circulation*, **1995**, *92(6)*, 1479.], post-ischaemic reperfusion injury, inflammatory disease of the central nervous system, inflammatory bowel disease, insulin resistance [Hotamisligil, G. S.; Shargill, N. S.; Spiegelman, B. M.; *et. al. Science*, **1993**, *259*, 87.] and HIV infection [Peterson, P. K.; Gekker, G.; *et. al. J. Clin. Invest.* **1992**, *89*, 574; Pallares-Trujillo, J.; Lopez-Soriano, F. J. Argiles, J. M. *Med. Res. Reviews*, **1995**, *15(6)*, 533.]], in addition to its well-documented antitumor properties [Old, L. *Science*, **1985**, *230*, 630.]. For example, research with anti-TNF-α antibodies and transgenic animals has demonstrated that blocking the formation of TNF-α inhibits the progression of arthritis [Rankin, E.C.; Choy, E.H.; Kassimos, D.; Kingsley, G.H.; Sopwith, A.M.; Isenberg, D.A.; Panayi, G.S. *Br. J. Rheumatol.* **1995**, *34*, 334; *Pharmaprojects*, **1996**, Therapeutic Updates *17 (Oct.)*, au197-M2Z.]. This

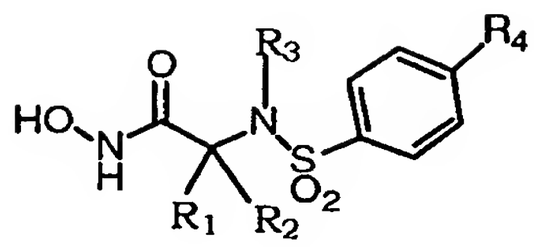
observation has recently been extended to humans as well as described in "TNF-α in Human Diseases", *Current Pharmaceutical Design*, **1996**, *2*, 662.

It is expected that small molecule inhibitors of TACE would have the potential for treating a variety of disease states. Although a variety of TACE inhibitors are known, many of these molecules are peptidic and peptide-like which suffer from bioavailability and pharmacokinetic problems. In addition, many of these molecules are non-selective, being potent inhibitors of matrix metalloproteinases and, in particular, MMP-1. Inhibition of MMP-1 (collagenase 1) has been postulated to cause joint pain in clinical trials of MMP inhibitors [*Scrip*, **1998**, *2349*, 20]. Long acting, selective, orally bioavailable non-peptide inhibitors of TACE would thus be highly desirable for the treatment of the disease states discussed above.

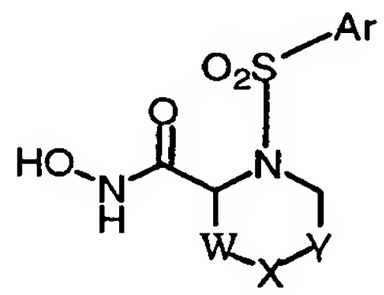
Examples of sulfonamide hydroxamic acid MMP/TACE inhibitors in which a 2 carbon chain separates the hydroxamic acid and the sulfonamide nitrogen, as shown below, are disclosed in WIPO international publications WO9816503, WO9816506, WO9816514 and WO9816520 and U. S. patent 5,776,961.



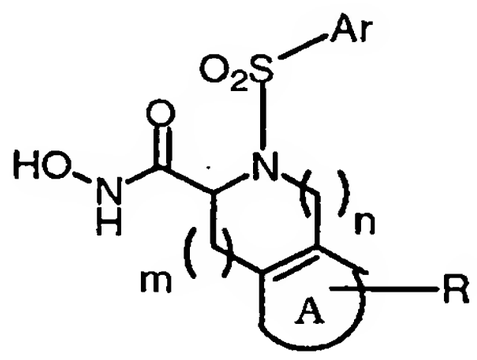

U. S. patents 5,455,258, 5,506,242, 5,552,419, 5,770,624, 5,804,593 and 5,817,822 as well as European patent application EP606,046A1 and WIPO international publications WO9600214 and WO9722587 disclose non-peptide inhibitors of matrix metalloproteinases and/or TACE of which the aryl sulfonamide hydroxamic acid shown below, in which 1 carbon separates the hydroxamic acid and the sulfonamide nitrogen, is representative. Additional publications disclosing sulfonamide based MMP inhibitors which are variants of the sulfonamide-hydroxamate shown below, or the analogous sulfonamide-carboxylates, are European patent applications EP-757037-A1 and EP-757984-A1 and WIPO international publications WO9535275, WO9535276, WO9627583, WO9719068, WO9727174, WO9745402, WO9807697, and WO9831664, WO9833768, WO9839313, WO9839329, WO9842659 and WO9843963. The discovery of this type of MMP inhibitor is further detailed by MacPherson, *et. al.* in *J. Med. Chem.*, (1997), 40, 2525 and Tamura, *et. al.* in *J. Med. Chem.* (1998), 41, 640.



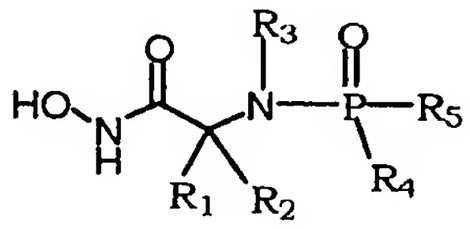
Publications disclosing β-sulfonamide-hydroxamate inhibitors of MMPs and/or TACE in which the carbon alpha to the hydroxamic acid has been joined in a ring to the sulfonamide nitrogen, as shown below, include U. S. patent 5,753,653, WIPO international publications WO9633172, WO9720824, WO9827069, WO9808815, WO9808822, WO9808823, WO9808825, WO9834918, WO9808827, Levin, *et. al. Bioorg. & Med. Chem. Letters* **1998**, *8*, 2657 and Pikul, *et. al. J. Med. Chem.* **1998**, *41*, 3568.



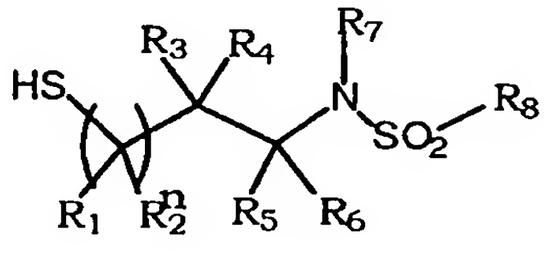
The patent applications DE19,542,189-A1, WO9718194, and EP803505 disclose additional examples of cylic sulfonamides as MMP and/or TACE inhibitors. In this case the sulfonamide-containing ring is fused to a aromatic or heteroaromatic ring.



Analogous to the sulfonamides are the phosphinic acid amide hydroxamic acid MMP/TACE inhibitors, exemplified by the structure below, which have been disclosed in WIPO international publication WO9808853.



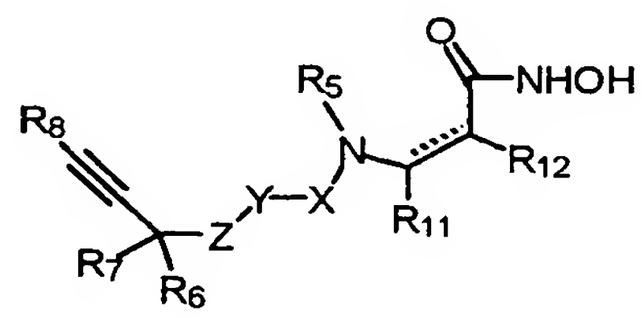
Sulfonamide MMP/TACE inhibitors in which a thiol is the zinc chelating group, as shown below, have been disclosed in WIPO international application 9803166.



It is an object of this invention to provide aryl sulfonamide and phosphinic acid amide hydroxamic acid MMP/TACE inhibitors in which the Y (the sulfonyl or phosphinyl aryl) is para-substituted with a substituted butynyl moiety or a propargylic ether, amine or sulfide. These compounds provide enhanced levels of inhibition of the activity of TACE in vitro and in a cellular assay and/or selectivty over MMP-1. These compounds may therefore be used in the treatment of diseases mediated by TNF.

## SUMMARY OF THE INVENTION

The TACE and MMP inhibiting ortho-sulfonamido hydroxamic acids of the present invention are represented by the formula:



**B**

where the C(=O)NHOH moiety and the $-NR_5-$ moiety are bonded to adjacent carbons;

wherein

X is $SO_2$ or $-P(O)R_{10}$;

Y is 5-10 membered heteroaryl ring having from 1-3 heteroatoms selected from N, $NR_9$, S and O, phenyl or naphthyl; with the proviso that X and Z may not be bonded to adjacent atoms of Y;

Z is O, NH, $CH_2$ or S;

$R_5$ is hydrogen or alkyl of 1-6 carbon atoms;

$R_6$ and $R_7$ are each, independently, hydrogen or methyl;

$R_8$ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, or phenyl;

$R_9$ is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or phenyl;

$R_{10}$ is alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, or 5-7 membered heteroaryl, having 1-3 heteroatoms selected from N, $NR_9$, S and O;

$R_{11}$ and $R_{12}$ are, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, or phenyl, and the optional double bond represented by the dotted line is present; or

$R_{11}$ and $R_{12}$, together with the carbons to which they are attached, form a 5-10 membered saturated or unsaturated mono or bicyclic alkyl ring optionally fused to one of a 5 to 7 membered saturated or unsaturated cycloalkyl ring, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, phenyl or napthyl rings; or

$R_{11}$ and $R_{12}$, together with the carbons to which they are attached form a 5-10 membered saturated or unsaturated mono- or bicyclic heterocycloalkyl having 1-2 heteroatoms selected from N, $NR_9$, S and O, optionally fused to one of a 5-7 membered mono or bi-cyclic heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered saturated or unsaturated cycloalkyl ring or a phenyl or napthyl ring;

the dotted line represents an optional double bond;

and n = 0-2; or a pharmaceutically acceptable salt thereof.

Preferred compounds of this invention include compounds of structure **B** wherein X is $SO_2$.

More preferred compounds of this invention include compounds of structure **B** wherein X is $SO_2$ and Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively.

More preferred compounds of this invention include compounds of structure **B** wherein X is $SO_2$,Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, and Z is oxygen.

More preferred compounds of this invention include compounds of structure **B** wherein X is $SO_2$,Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, Z is oxygen and $R_6$ and $R_7$ are hydrogen.

More preferred compounds of this invention include compounds of structure **B** wherein X is $SO_2$,Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively, Z is oxygen, $R_6$ and$R_7$ are hydrogen and $R_8$ is -$CH_2OH$ or methyl.

Still more preferred compounds of the present invention are (1R,2R)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxycyclohexanecarboxamide;

(1R, 2R)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide;

3-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxypropanamide;

3-({[4-(2-Butynyloxy)phenyl]sulfonyl} (methyl) amino)-N-hydroxypropanamide;

(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclopentanecarboxamide;

(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl} (methyl) amino] N-hydroxycyclopentanecarboxamide;

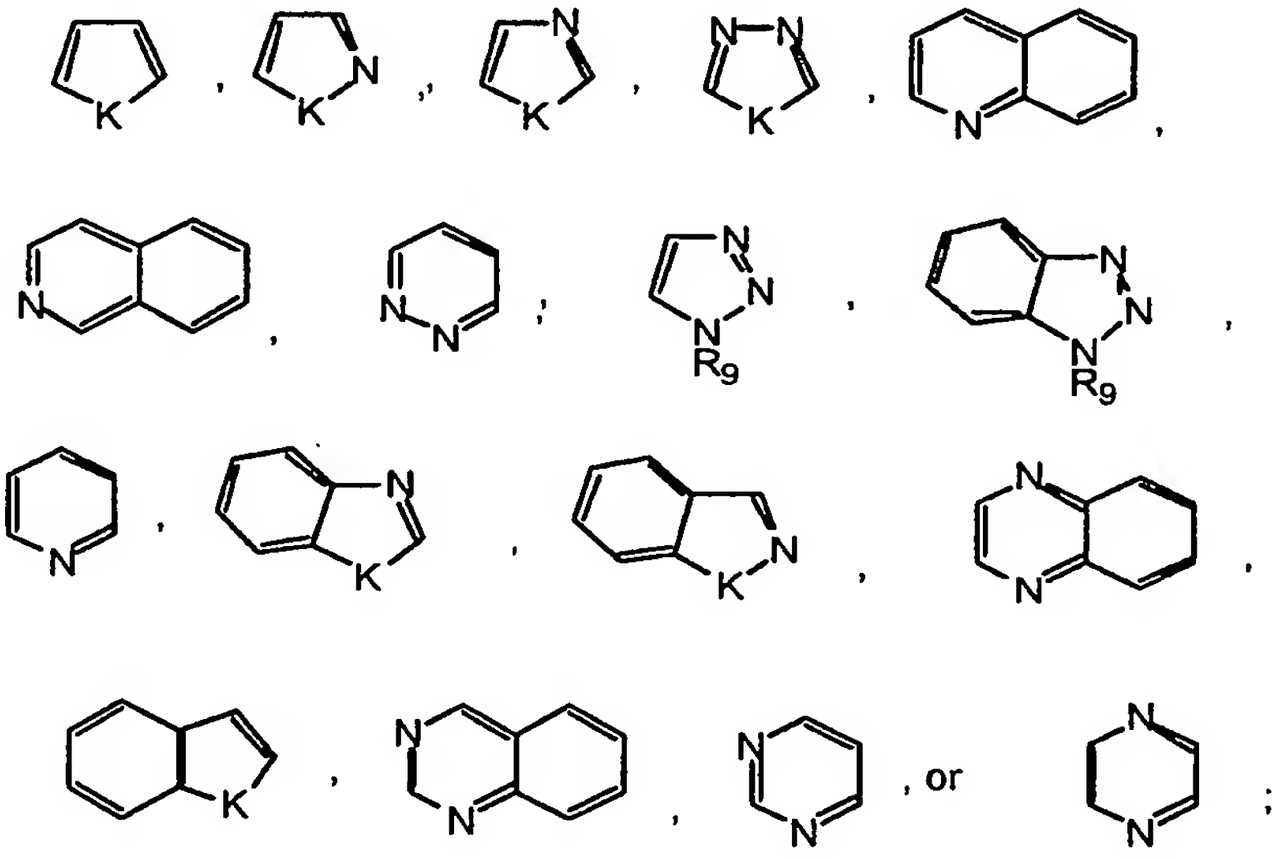
(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide;

(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino]-N-hydroxycyclohexanecarboxamide;

(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxybicyclo [2.2.1] heptane-2-carboxamide; and

(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino)-N-hydroxybicyclo [2.2.1] heptane-2-carboxamide.

Heteroaryl, as used throughout, is a 5-10 membered mono- or bicyclic ring having from 1-3 heteroatoms selected from N, $NR_9$, S and O. Heteroaryl is preferably

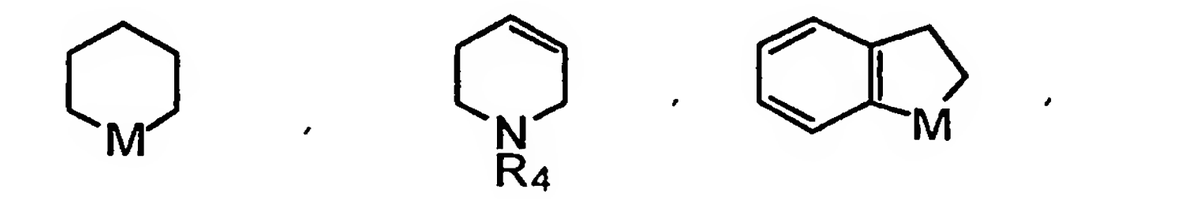


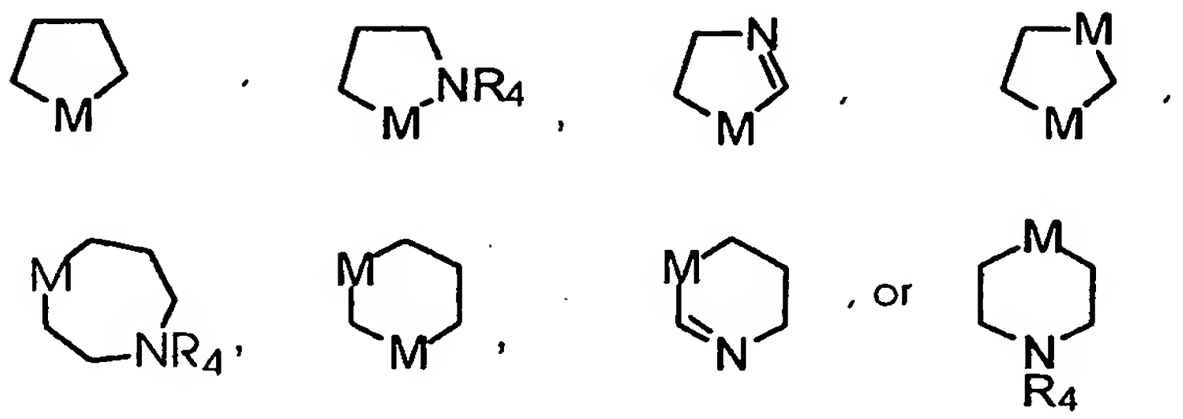
wherein K is $NR_9$, O or S and $R_9$ is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or phenyl. Preferred heteroaryl rings include pyrrole, furan, thiophene, pyridine, pyrimidine, pyridazine, pyrazine, triazole, pyrazole, imidazole, isothiazole, thiazole, isoxazole, oxazole, indole, isoindole, benzofuran, benzothiophene, quinoline, isoquinoline, quinoxaline, quinazoline, benzotriazole, indazole, benzimidazole, benzothiazole, benzisoxazole, and benzoxazole.

Heteroaryl groups of the present invention may optionally be mono- or di-substituted.

Heterocycloalkyl as used herein refers to a 5 to 10 membered saturated or unsaturated mono or bi-cyclic ring having 1 or 2 heteroatoms selected from

N, $NR_4$, S or O. Heterocycloalkyl rings of the present invention are preferably selected from





wherein M is $NR_4$, O or S and $R_4$ is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, heteroaryl, $-S(O)_nR_2$, $-COOR_2$, $-CONR_2R_3$, $-SO_2NR_2R_3$ or $-COR_2$. Preferred heterocycloalkyl rings include piperidine, piperazine, morpholine, tetrahydropyran, tetrahydrofuran or pyrrolidine. Heterocycloalkyl groups of the present invention may optionally be mono- or di-substituted.

Aryl, as used herein refers to phenyl or naphthyl which may, optionally be mono-, di- or tri-substituted.

Alkyl, alkenyl, alkynyl, and perfluoroalkyl include both straight chain as well as branched moieties. Alkyl, alkenyl, alkynyl, and cycloalkyl groups may be unsubstituted (carbons bonded to hydrogen, or other carbons in the chain or ring) or may be mono- or poly-substituted. Cycloalkyl groups may be mono or bicyclic. Examples of monocyclic cycloalkyl groups include cyclopentyl and cyclohexyl. Examples of bicyclic cycloalkyl groups include bicycloheptane and adamantyl.

Halogen means bromine, chlorine, fluorine, and iodine.

Suitable substituents of aryl, heteroaryl, alkyl, alkenyl, alkynyl, and cycloalkyl include, but are not limited to halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cyclocalkyl of 3-6 carbon atoms, $-OR_2$, -CN, $-COR_2$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_2R_3$, $-S(O)_nR_2$ $-OPO(OR_2)OR_3$, $-PO(OR_2)R_3$, $-OC(O)NR_2R_3$, $-C(O)NR_2OR_3$, $-COOR_2$, $-SO_3H$, $-NR_2R_3$, $-N[(CH_2)_2]_2NR_2$, $-NR_2COR_3$, $-NR_2COOR_3$, $-SO_2NR_2R_3$, $-NO_2$, $-N(R_2)SO_2R_3$, $-NR_2CONR_2R_3$, $-NR_2C(=NR_3)NR_2R_3$,$-NR_2C(=NR_3)N(SO_2)R_2R_3$, $NR_2C(=NR_3)N(C=O)R_2R_3$, $-SO2NHCOR_4$, $-CONHSO2R_4$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO2NHCONR_2R_3$, phenyl, naphthyl, heteroaryl or heterocycloalkyl;

wherein $-NR_2R_3$ may form a pyrrolidine, piperidine, morpholine, thiomorpholine, oxazolidine, thiazolidine, pyrazolidine, piperazine, or azetidine ring;

$R_2$ and $R_3$ are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, heteroaryl or heterocycloalkyl;

$R_4$ is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, heteroaryl, $-S(O)_nR_2$, $-COOR_2$, $-CONR_2R_3$, $-SO_2NR_2R_3$ or $-COR_2$ ; and n is 0-2.

Suitable substituents of heterocycloalkyl groups of the present invention include, but are not limited to alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, heteroaryl and heterocycloalkyl.

When a moiety contains more than one substituent with the same designation each of those substituents may be the same or different.

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic,

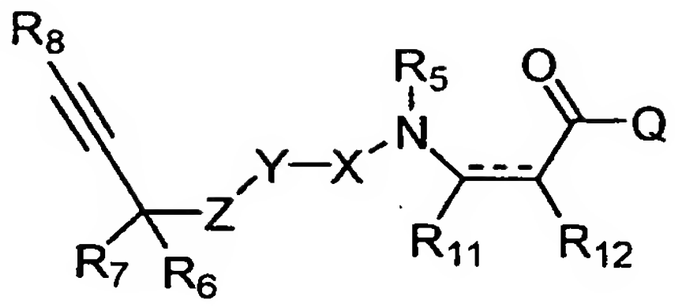
malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this invention contains a basic moiety. Salts may also be formed from organic and inorganic bases, preferably alkali metal salts, for example, sodium, lithium, or potassium, when a compound of this invention contains an acidic moiety.

The compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. It is recognized that one optical isomer, including diastereomer and enantiomer, or stereoisomer may have favorable properties over the other. Thus when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

The compounds of this invention are shown to inhibit the enzymes MMP-1, MMP-9, MMP-13 and TNF-α converting enzyme (TACE) and are therefore useful in the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, graft rejection, insulin resistance, bone disease and HIV infection. In particular, the compounds of the invention provide enhanced levels of inhibition of the activity of TACE in vitro and in cellular assay and/or enhanced selectivity over MMP-1 and are thus particularly useful in the treatment of diseases mediated by TNF.

Accordingly this invention provides a process for preparing compounds of formula 1, as defined above, which comprises one of the following:

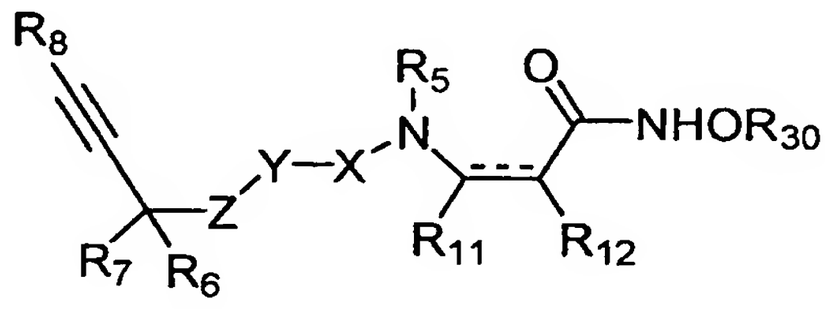
a) reacting a compound of formula V:



(V)

wherein $R_5$ $R_6$, $R_7$, $R_8$, and $R_{11}$ $R_{12}$, X, Y, Z and the dotted line are defined above, and Q is OH or a reactive derivative thereof, with hydroxylamine to give a corresponding compound of formula **B**;

b) deprotecting a compound of formula VI:



(VI)

wherein $R_5$ $R_6$, $R_7$, $R_8$, $R_{11}$ $R_{12}$, X, Y, Z and the dotted line are defined above, and $R_{30}$ is a suitable protecting group such as t-butyl, benzyl, and trialkylsilyl, to give a corresponding compound of formula **B**

c) resolving a mixture (e.g. racemate) of optically active isomers of a compound of formula **B** to isolate one enantiomer or diastereomer substantially free of the other enantiomer or diastereomers;

d) acidifying a basic compound of formula **B** with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt.

With regards to process a) the reaction can be carried out by processes known in the art e.g. by reaction of the acid chloride reactive derivative with hydroxylamine.

Removal of protecting groups, as illustrated by process b) can be carried out by processes known in the art to provide the hydroxamic acid.

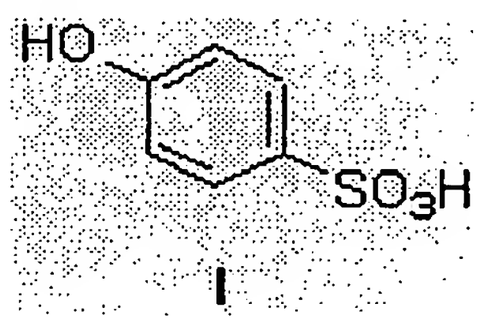
With regard to process c) standard separation techniques may be used to isolate particular enantiomeric or diastereomeric forms. For example a racemic mixture may

be converted to a mixture of optically active diastereoisomers by reaction with a single enantiomer of a 'resolving agent' (for example by diastereomeric salt formation or formation of a covalent bond). The resulting mixture of optically active diastereoisomers may be separated by standard techniques (e.g. crystallisation or chromatography) and individual optically active diastereoisomers then treated to remove the 'resolving agent' thereby releasing the single enantiomer of the compound of the invention. Chiral chromatography (using a chiral support, eluent or ion pairing agent) may also be used to separate enantiomeric mixtures directly.

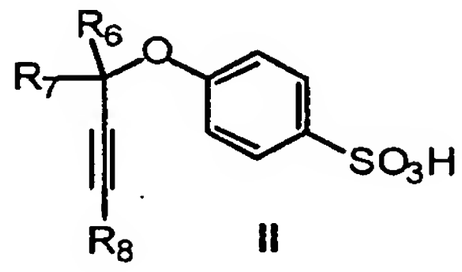
The compounds of formula **B** may be isolated in the form of a salt of a pharmaceutically acceptable acid e.g. an organic or inorganic acid by treatment with an acid such as described above.

The invention is further directed to a process for making compounds of structure **B** involving one or more reactions as follows:

1) alkylating a compound of formula **I**, or a salt or solvate thereof,

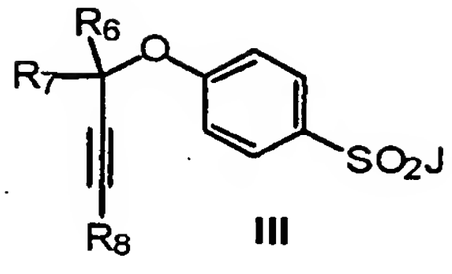



into a compound of formula **II**




**II**

2) reacting a compound of formula **II** above, or a salt or solvate thereof, with a chlorinating agent such as thionyl chloride, chlorosulfonic acid, oxalyl chloride, phosphorus pentachloride, or other halogenating agents such as fluorosulfonic acid or thionyl bromide to a compound of formula **III**:



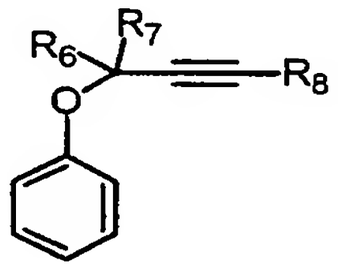
III

wherein J is fluorine, bromine, chlorine.

The resultant sulfonyl chloride, fluoride or bromide, may be further converted into triazolide, imidazolide or benzothiazolide derivatives, where J is 1,2,4-triazolyl, imidazol-yl or benzotriazolyl, by reacting the compound with 1,2,4-triazole, imidazole or benzotriazole, respectively. $R_6$, $R_7$ and $R_8$ are as defined above.

The invention is still further directed to a process for making compounds of structure **B** involving one or more reactions as follows:

1) alkylating phenol, or a salt or solvate thereof, into a compound of formula **IV**:



**IV**

2) reacting a compound of formula **IV** above, or a salt or solvate thereof with chlorosulfonic acid to prepare a compound of formula **II** above.

Particularly preferred intermediates are compounds of formulae **II** and **III**, with the proviso that $R_6$ is not hydrogen.

The invention compounds are prepared using conventional techniques known to those skilled in the art of organic synthesis. The starting materials used in preparing the compounds of the invention are known, made by known methods or are commercially available.

Those skilled in the art will recognize that certain reactions are best carried out when other potentially reactive functionality on the molecule is masked or

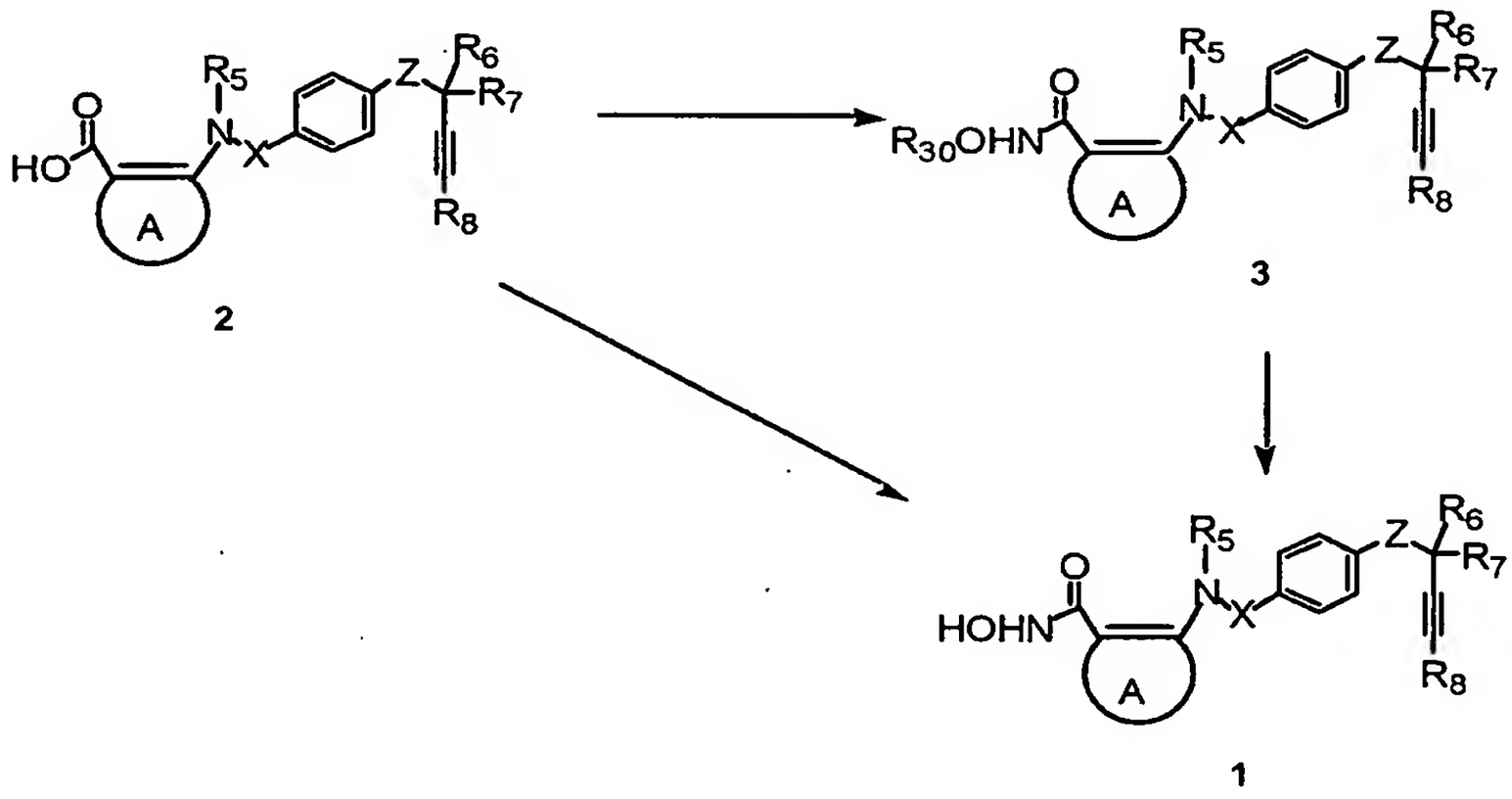
protected, thus avoiding undesirable side reactions and/or increasing the yield of the reaction. To this end, those skilled in the art may use protecting groups. Examples of these protecting group moieties may be found in T. W. Greene, P. G. M. Wuts "Protective Groups in Organic Synthesis", 2nd Edition, 1991, Wiley & Sons, New York. Reactive side chain functionalities on amino acid starting materials are preferably protected. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxy, amino, carboxy, etc.), the structure and stability of the molecule of which the substituent is part and the reaction conditions.

When preparing or elaborating compounds of the invention containing aryl, heteroaryl or heterocyclic rings, those skilled in the art recognize that substituents on that ring may be prepared before, after or concomitant with construction of the ring. For clarity, substituents on such rings have been omitted from the schemes herein below.

Those skilled in the art will recognize that the nature and order of the synthetic steps presented may be varied for the purpose of optimizing the formation of the compounds of the invention.

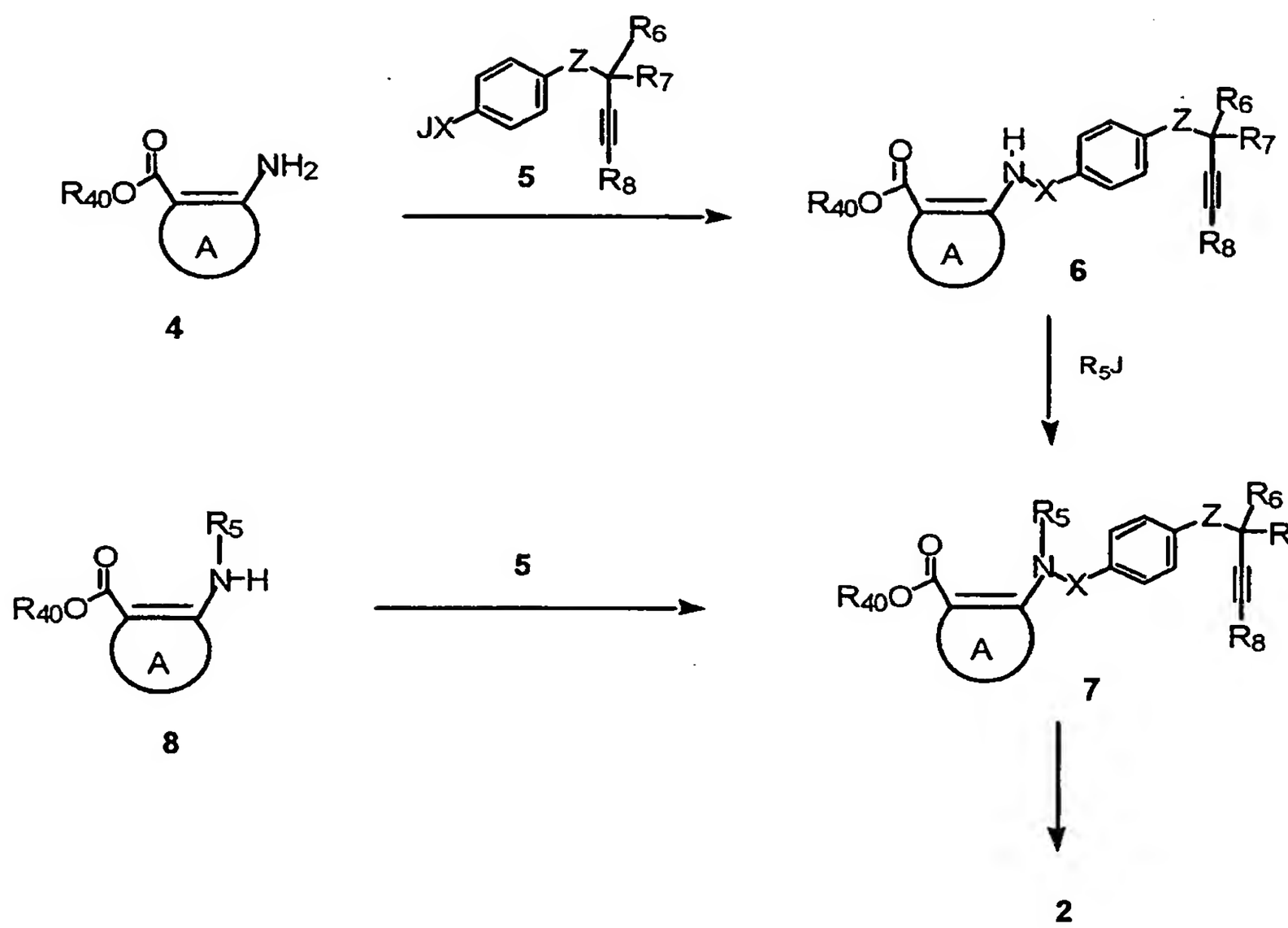
The hydroxamic acid compounds of the invention, **1**, are prepared according to **Scheme 1** by converting a carboxylic acid, **2** wherein A = $R_{11}$ and $R_{12}$, into the corresponding acid chloride or anhydride, or by reacting it with a suitable peptide coupling reagent, followed by reaction with hydroxylamine to give **1**, or with a protected hydroxylamine derivative to give **3**. Compounds **3**, wherein $R_{30}$ is a t-butyl, benzyl, trialkylsilyl or other suitable masking group may then be deprotected by known methods to provide the hydroxamic acid **1**.

Scheme 1:




Carboxylic acids **2** may be prepared as shown in **Scheme 2**. Amino acid derivative **4**, in which $R_{40}$ is hydrogen or a suitable carboxylic acid protecting group, may be sulfonylated or phosphorylated by reacting with compounds **5**, in which J is a suitable leaving group including, but not limited to chlorine. The N-H compound **6** may then be alkylated with $R_3J$ and a base such as potassium carbonate or sodium hydride in a polar aprotic solvent such as acetone, N,N-dimethylformamide (DMF), or tetrahydrofuran (THF) to provide sulfonamide **7**. Compound **7** is also available through direct reaction of **5** with an N-substituted amino acid derivative, **8**. Conversion of **7** into the carboxylic acid is performed by acid, base hydrolysis, or other method consistent with the choice of protecting group $R_{40}$ and the presence of a carbon-carbon triple bond.

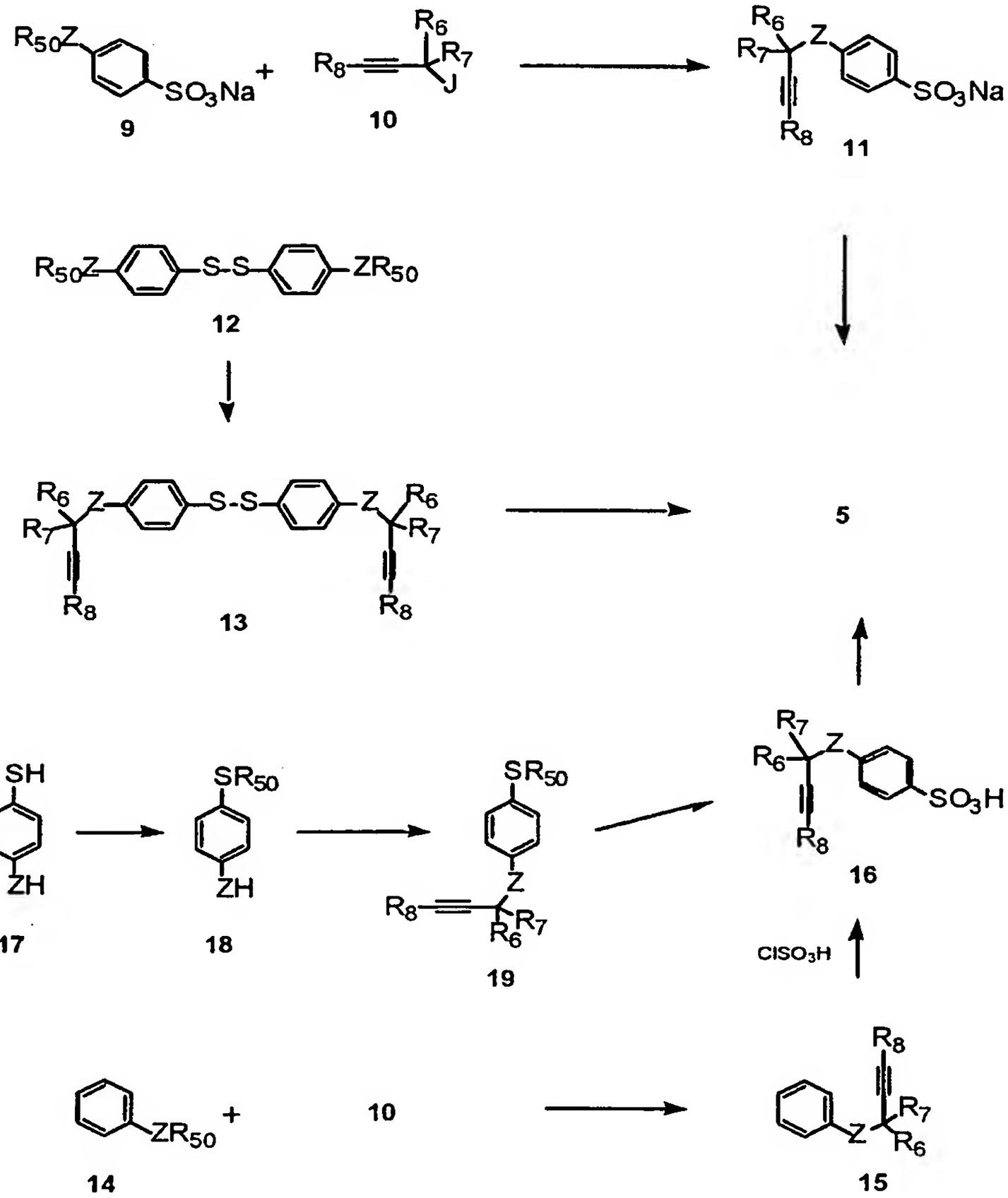
Scheme 2:




Methods of preparation of sulfonylating agents **5** are shown in **Scheme 3**. Thus, sulfonic acid salts **9**, where $ZR_{50}$ is a hydroxy, thiol or substituted amino moiety may be alkylated with acetylenes **10**, where J is a suitable leaving group such as halogen mesylate, tosylate, or triflate to give **11**. Acetylenes **10** are commercially available or known compounds, or they may be synthesized by known methods by those skilled in the art. The sulfonic acid salts **11** may be converted into the corresponding sulfonyl chloride or other sulfonylating agent **5** by known methods, such as reaction with oxalyl chloride or other reagent compatible with substituents $R_6$, $R_7$ and $R_8$ and the acetylene. Alternatively, the disulfide **12** may be converted into di-acetylene **13** by reaction with compounds **10**, followed by reduction of the disulfide bond to provide the analogous thiols which may be converted into **5** by known methods. Alkylation of the phenol, thiophenol, aniline or protected aniline **14** with **10** to give **15**, followed by reaction with chlorosulfonic acid provide sulfonic acids **16** which are readily converted into **5** with oxalyl chloride or similar reagents.

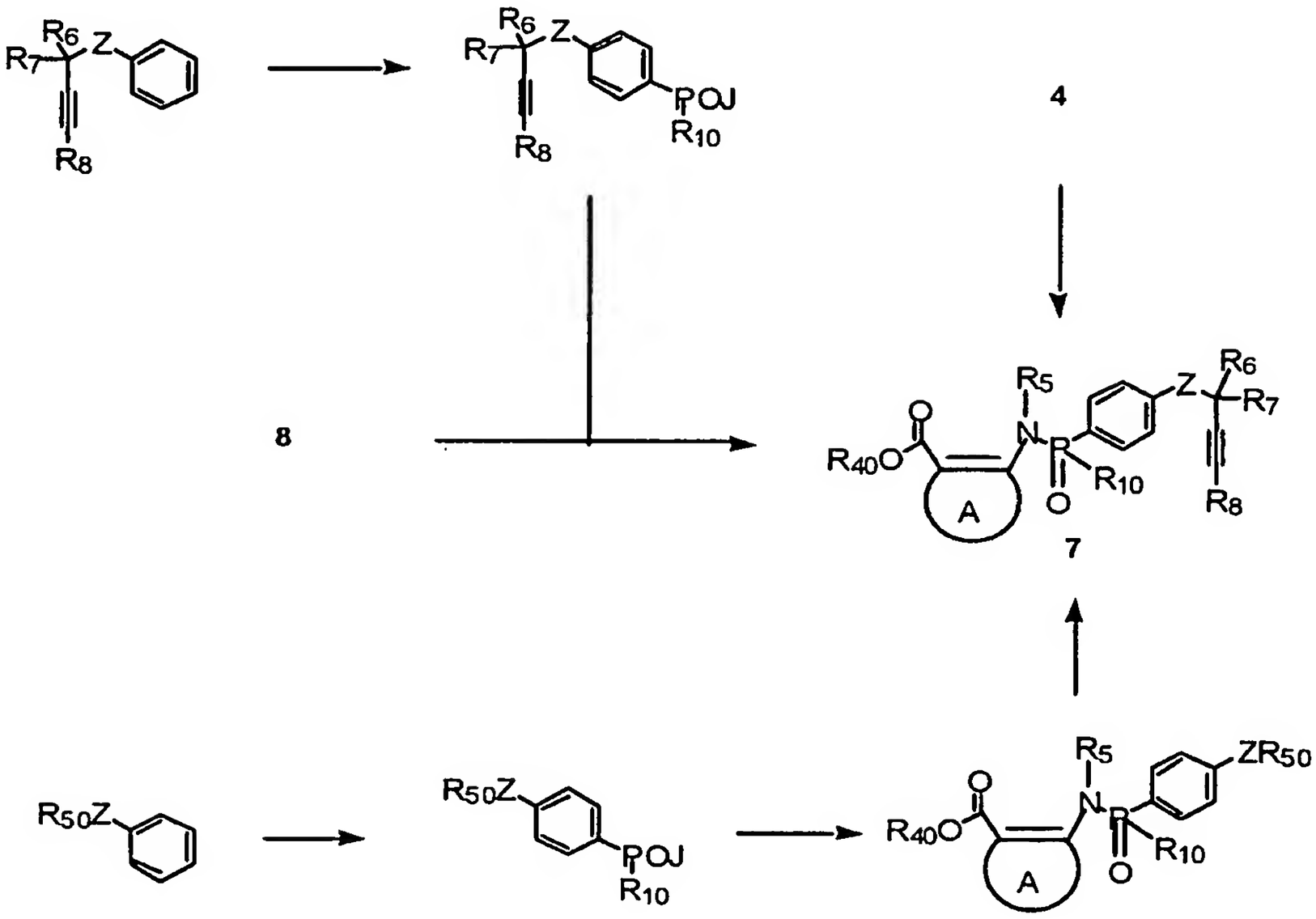
Thiophenols **17** are also precursors to **5** via protection of the thiol, alkylation of ZH, where Z is O, N or S, and deprotection of the sulfur followed by oxidation to the sulfonic acid **16**.

Scheme 3:



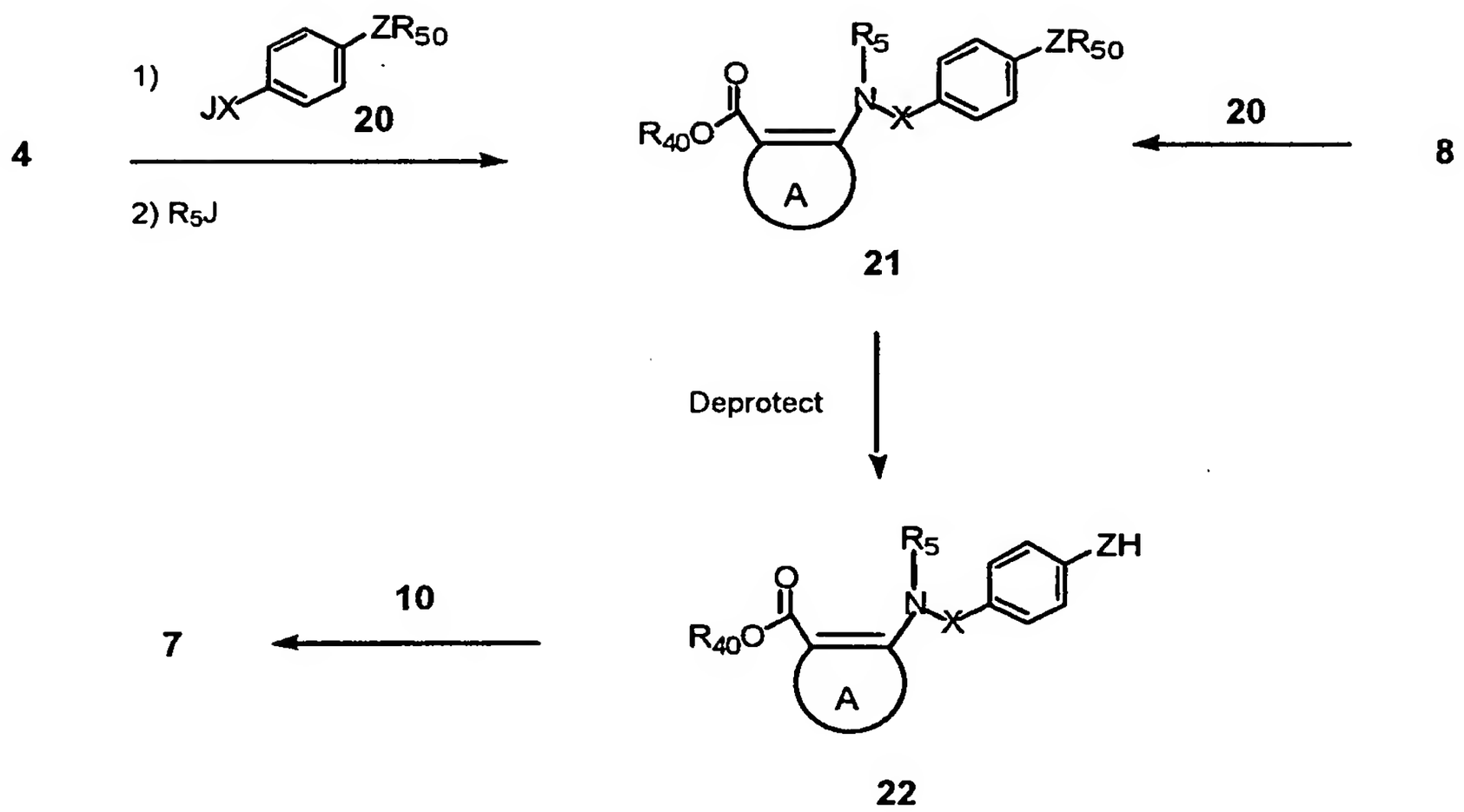

The phosphorus containing analogs of **8** may be prepared using similar methodology, as shown in **Scheme 4**.

Scheme 4:



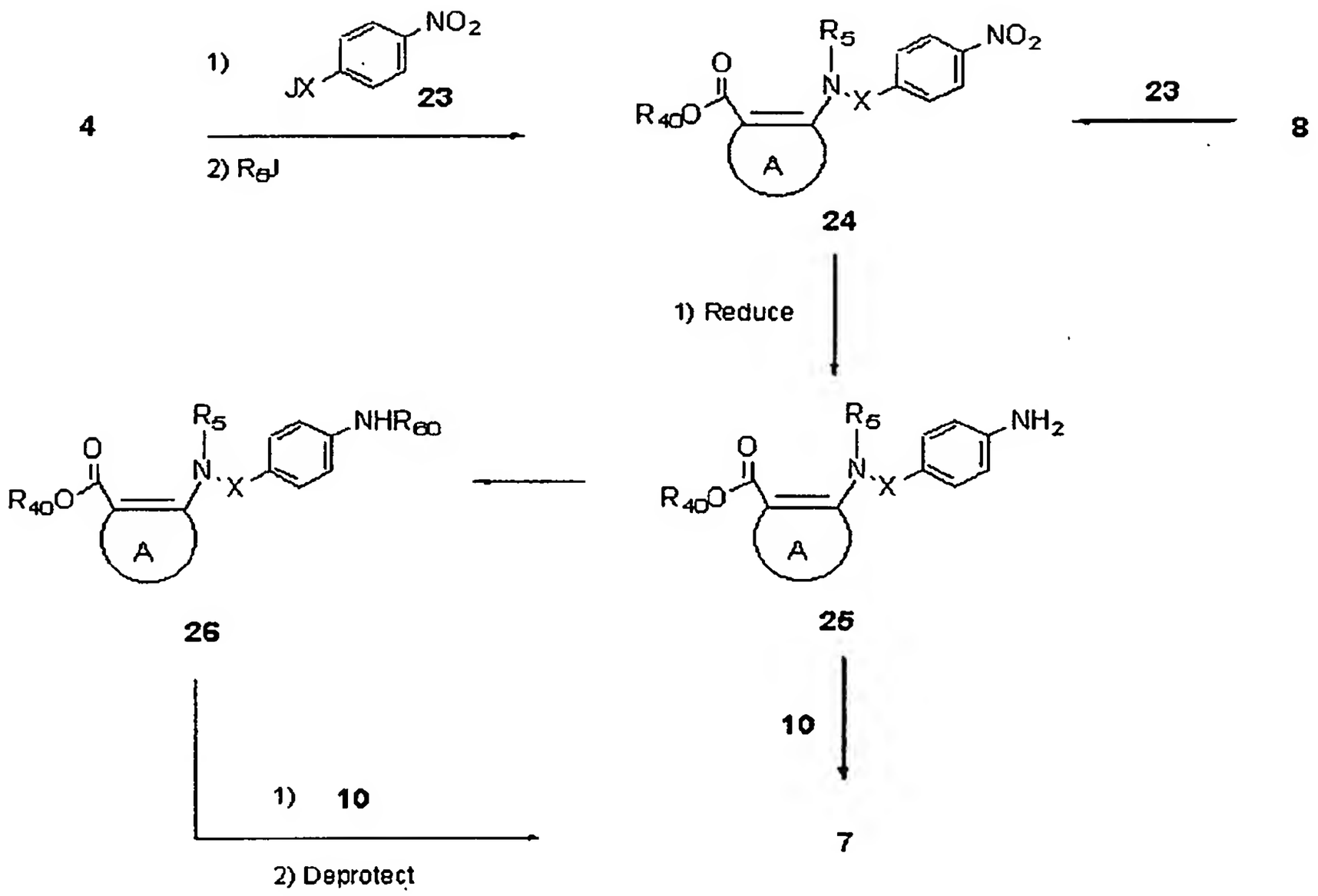

The acetylenic side chain may also be appended after sulfonylation or phosphorylation of the amino acid derivative, as shown in **Scheme 5**. Thus, the amino acid derivatives **4** and **8** can be sulfonylated or phosphorylated with compounds **20**, where $ZR_{50}$ is hydroxy or protected hydroxy, thiol or amine, and, if necessary, alkylated with $R_7J$ as in **Scheme 2**, to give **21**. Removal of the $R_{50}$ masking group to give **22** and subsequent alkylation of the resulting phenol, thiol or amine with **10** provides **7**. In the case where $ZR_{50}$ is equal to OH, no deprotection step is required to give **22**.

Scheme 5:



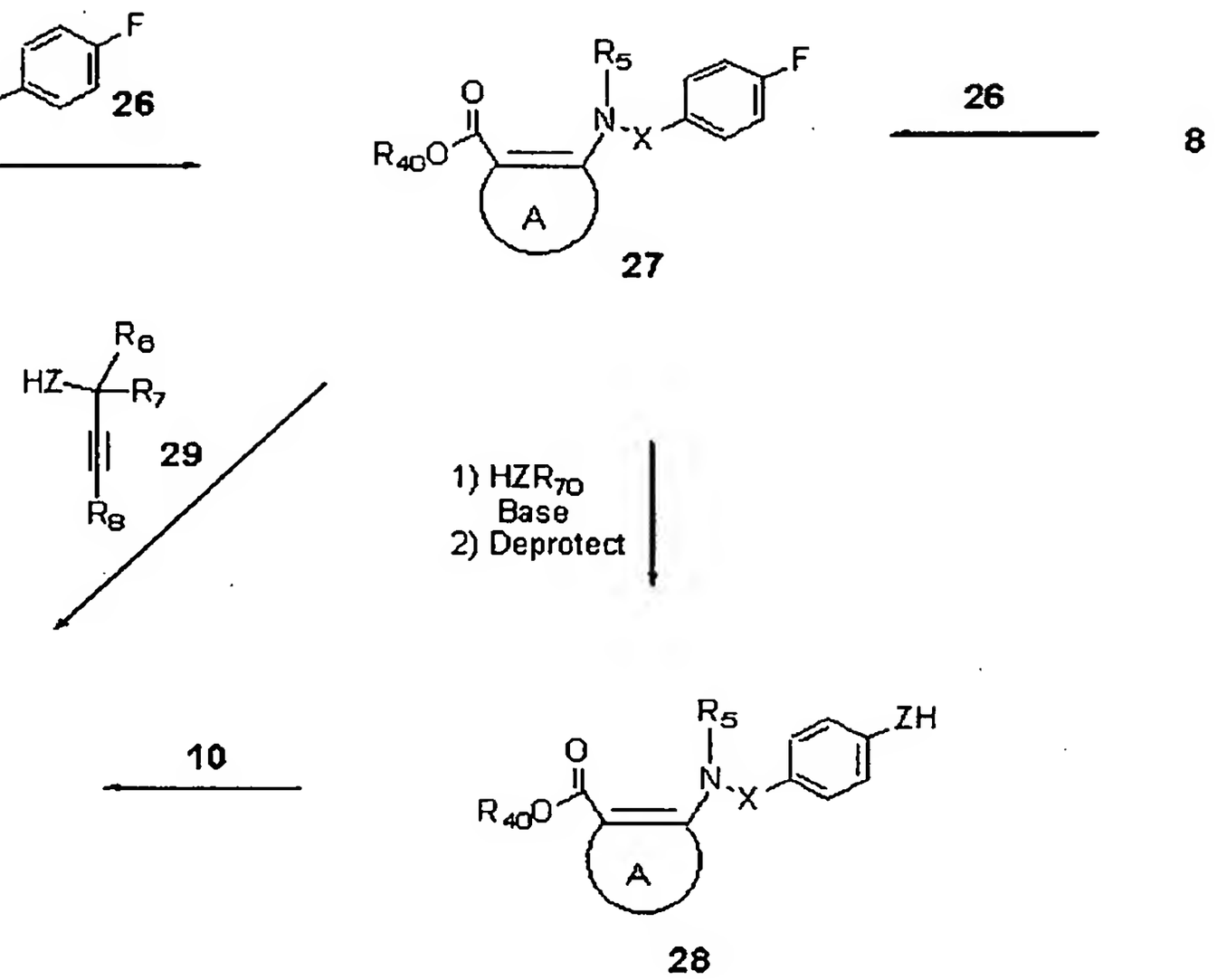

The propargylic amine analogs of **7** can be synthesized as shown in **Scheme 6** starting from the amino acid derivatives **4** and/or **8**. Sulfonylation or phosphorylation with para-nitro aryl compound **23**, for example 4-nitrobenzenesulfonyl chloride, followed by alkylation with $R_5J$ (for **4**) using a base such as potassium carbonate or sodium hydride in DMF provides **24**. Reduction of the nitro moiety with hydrogen and palladium on carbon, tin chloride or other known method to give aniline **25** and subsequent alkylation with **10** then provides **7**. Aniline **25** may be derivatized with a suitable nitrogen protecting group, such as t-butoxycarbonyl, to give **26** prior to alkylation with **10** subsequent deprotection after the alkylation step.

Scheme 6:



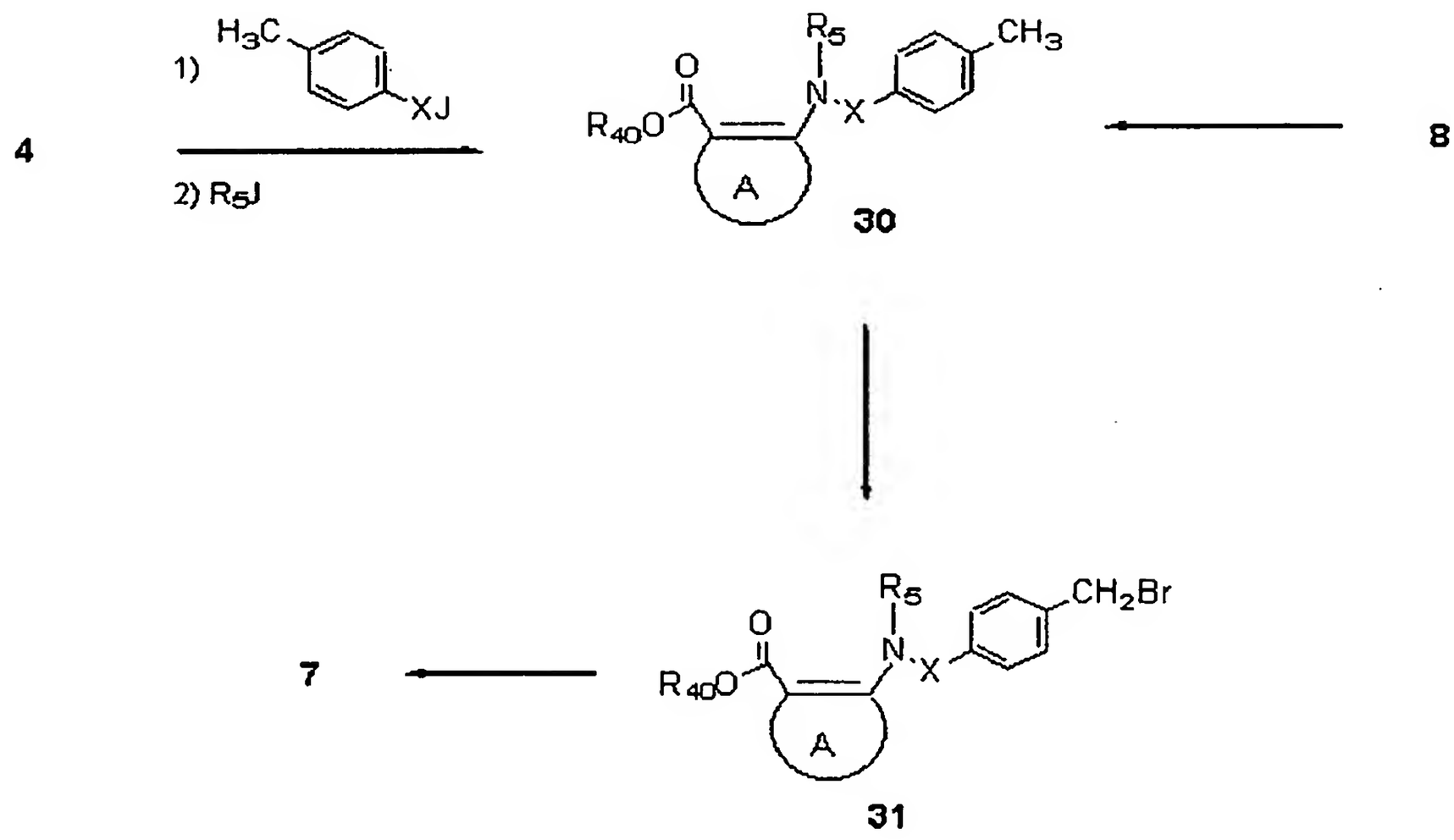

Acetylenic derivatives **7** are also accessible via the fluoro compounds **27**, readily prepared from the amino acid derivatives **4** and/or **8** by reaction with fluoraryl **26,** as shown in **Scheme 7**. Displacement of the fluorine of **27** in the presence of a base such as sodium hydride with a masked hydroxy, thiol, or amino group ($HZR_{70}$, where $R_{70}$ is a suitable protecting group) in a polar aprotic solvent such as DMF, followed by deprotection gives **28**, which can then be alkylated with **10** to provide **7**. Conversion of **27** to **28**, where Z is sulfur, might also be accomplished with $Na_2S$, $K_2S$, NaSH or KS(C=S)OEt. The fluorine of **27** can also be displaced in a polar aprotic solvent with the propargylic derivative **29**, where Z is O, S or NH, in the presence of a base such as sodium hydride, to give **7** directly.

Scheme 7:




Compound **7**, wherein Z is a methylene group, is available via **30**, as shown in **Scheme 8**. Benzylic bromination of **30** with N-bromosuccinimide in a chlorinated hydrocarbon solvent provides bromide **31**. This is followed by displacement of the bromide with the appropriate propynyl cuprate to provide sulfonamide **8**.

Scheme 8:




Compounds of the invention can also be prepared by modifying substituents on the acetylenic side chain at any stage after sulfonylation or phosphorylation of the starting amino acid derivatives **4** or **8**. Functional groups such as halogen, hydroxy, amino, aldehyde, ester, ketone, etc. may be manipulated by standard methods to form the moieties defined by $R_1$-$R_8$ of compounds **1**. It is recognized by those skilled in the art of organic synthesis that the successful use of these methods is dependent upon the compatibility of substituents on other parts of the molecule. Protecting groups and/or changes in the order of steps described herein may be required.

Some of the methods available for the derivatization of compounds of structure **32** (equivalent to compound **7** wherein $R_{12}$ is hydrogen) are shown in **Scheme 9**. Metallation of the terminal acetylene **32** followed by addition of an aldehyde or alkyl halide, sulfonate or triflate provides derivatives **33** and **34**. Reaction of **32** with formaldehyde and an amine provides the Mannich addition product **35**. Cyanogen bromide addition to **35** gives the propargylic bromide **36** which may be displaced with a variety of nucleophiles to give, for example, ethers, thioethers and amines **37**. Palladium catalyzed coupling reactions of **32** provide the aryl or heteroaryl acetylenes **38**. It is recognized by those skilled in the art of organic

synthesis that the successful use of these methods is dependent upon the compatibility of substituents on other parts of the molecule. Protecting groups and/or changes in the order of steps described herein may be required, and $R_{35}$, $R_{45}$, $R_{55}$, $R_{65}$ and $R_{75}$ are alkyl, e.g. methyl;

Scheme 9:

The following specific examples illustrate the preparation of representative compounds of this invention. The starting materials, intermediates, and reagents are either commercially available or can be readily prepared following standard literature procedures by one skilled in the art of organic synthesis.

**Example 1**

**(trans)-2-(4-Methoxybenzenesulfonyl)aminocyclohexanecarboxylic acid**

To a room temperature solution of 1g (6.8 mmol) of trans-2-amino-1-cyclohexylcarboxylic acid in 50 ml of dioxane:$H_2O$ (1:1) containing 1.7 ml (12.2 mmol) of triethylamine was added 1.54g ( 7.46 mmol) of 4-methoxybenzenesulfonyl chloride. The mixture was stirred at 25 °C for 18 h. The resulting mixture was diluted with pentane to afford 1.119 g (51%) of the desired sulfonamide product as a white solid. $^1$H NMR(DMSO-$d_6$): 7.7 ppm (dd, 2H, Ar), 7.4 ppm (d, 1H, NH), 7.0 ppm (dd, 2H, Ar), 3.8 ppm (s, 3H, OMe), 3.5 ppm (m, 1H, N-CH), 1.0-1.7 ppm (m, 9H, hydrocarbon).

**Example 2**

**(cis)-2-(4-Methoxybenzenesulfonyl)aminocyclohexanecarboxylic acid**

In the same manner as described in Example 1, 2.5 g (17 mmol) of cis-2-amino-1-cyclohexylcarboxylic acid provided 3.283 g (60%) of the desired carboxylic acid. Electrospray Mass Spec 314.1 $(M+H)^+$.

**Example 3**

**(trans)-2-(4-Methoxybenzenesulfonyl)aminocyclohexane-carboxylic acid t-butyl ester**

To a solution of 0.313g (1 mmol) of the product from Example 1 in 5.0 mL of toluene was added 1 mL (4 mmol) of N,N-dimethylformamide di-tert-butyl acetal. The resulting mixture was heated at 110 •C for 4h under nitrogen and then allowed to cool to room temperature. The solution was then poured on top of a silica gel column. Chromatography on silica gel eluting with 10-20% ethyl acetate/hexane gave 353 mg (96%) of the desired ester as a white solid. $^1$H NMR($CDCl_3$): 7.8 ppm (dd, 2H, Ar), 7.0 ppm (dd, 2H, Ar), 5.7 ppm (d, 1H, NH), 3.9 ppm (s, 3H, OMe), 3.4 ppm (m, 1H, N-CH), 2.5 ppm (m, 1H, CH-$CO_2$-), 1.0-2.0 ppm (m, 17H, hydrocarbon).

**Example 4**

**(cis)-2-(4-Methoxy-benzenesulfonylamino)-cyclohexanecarboxylic acid tert-butyl ester**

In the same manner as described in Example 3, 1.438 g (4.59 mmol) of the product from Example 2 provided 0.739 g (44%) of the desired tert-butyl ester as a colorless oil. Electrospray Mass Spec 370.1 $(M+H)^+$.

**Example 5**

**(trans)-2-[Benzyl-(4-methoxybenzenesulfonyl)amino]-cyclohexanecarboxylic acid t-butyl ester**

To a solution of 1.146 g (3.1 mmol) of the product from Example 3 in 31 mL of DMF was added 0.137g (3.42 mmol) of 60% sodium hydride. The resulting mixture was stirred for 30 min at 25°C and then 0.42 mL (3.50 mmol) of benzyl bromide was added all at once. This reaction mixture was stirred for 10 hr at 55 •C and then poured into water and extracted with ether. The combined organics were washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to provide a white solid which was recrystallized from ethyl acetate/Hexanes to provide 1.364 g (95%) of the desired product. $^1H$ NMR($CDCl_3$): 7.7 ppm (dd, 2H, Ar), 7.1-7.4 (m, 5H, Ar), 6.9 ppm (dd, 2H, Ar), 4.5-4.7 ppm (AB quartet, 2H, $CH_2$-Ar), 3.9 ppm (s, 3H, OMe), 4.0 ppm (m, 1H, N-CH), 2.9 ppm (m, 1H, CH-$CO_2$-), 1.0-2.3 ppm (m, 17H, hydrocarbon protons).

**Example 6**

**(cis)-2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-cyclohexanecarboxylic acid tert-butyl ester**

In the same manner as described in Example 5, 0.600 g (1.62 mmol) of the product from Example 4 provided 0.310 g (42%) of the desired benzylated ester as a colorless oil. Electrospray Mass Spec 460.1 $(M+H)^+$.

**Example 7**

**(trans)-2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]- cyclohexanecarboxylic acid**

To a solution of 1.364 g (2.97 mmol) of the product from Example 5 in 10mL of dichloromethane was added 10mL of trifluoroacetic acid and the mixture was stirred for 4h at room temperature. The solvent was then concentrated in vacuo and the residue was chromatographed on silica gel eluting with 10-100% ethyl

acetate/hexane to provide 1.092 g (73%) of the desired product as a white solid. Electrospray Mass Spec 404.2 $(M+H)^+$

**Example 8**

**(cis)-2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-cyclohexanecarboxylic acid**

In the same manner as described in Example 7, 0.240 g (0.522 mmol) of the product from Example 6 provided 0.207 g (98%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec 404.0 $(M-H)^-$.

**Example 9**

**4-But-2-ynyloxy-benzenesulfonic acid sodium salt**

To a solution of 52.35g (0.225 mol) of 4-hydroxybenzenesulfonate sodium salt in 1L of isopropanol and 225 mL of a 1.0N solution of sodium hydroxide was added 59.96g (0.45 mol) of 1-bromo-2-butyne. The resulting mixture was heated to 70° for 15h and then the isopropanol was removed by evaporation in vacuo. The resulting white precipitate was collected by filtration, washed with isopropanol and ether and dried in vacuo to give 56.0g (100%) of the butynyl ether as a white solid.

**Example 10**

**4-But-2-ynyloxy-benzenesulfonyl chloride**

To a 0° solution of 43.8 mL (0.087 mol) of 2M oxalyl chloride/dichloromethane solution in 29 mL of dichloromethane was dropwise added 6.77 mL (0.087 mol) of DMF followed by 7.24g (0.029 mol) of the product of Example 9. The reaction mixture was stirred for 10 minutes at 0° then let warm to room temperature and stirred for 2 days. The reaction was then poured into ice and extracted with 150 mL of hexanes. The organics were washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated in vacuo to provide 6.23g (88%) of the sulfonyl chloride as a yellow solid; m.p. 63-65°C. EI Mass Spec: 243.9 $(M^+)$.

**Example 11**

**But-2-ynyloxy-benzene**

To a solution of 6.14g (0.023 mol) of triphenylphosphine dissolved in 100 mL of benzene and 40 mL of THF was added 1.75 mL (0.023 mol) of 2-butyn-1-ol. After five minutes 2.00 (0.023 mol) phenol, dissolved in 10 mL of THF, was added to the reaction followed by 3.69 mL (0.023 mol) of diethyl azodicarboxylate. The resulting reaction mixture was stirred for 18h at room temperature and then concentrated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate/hexanes (1:10) to provide 2.18g (70%) of the butynyl ether as a clear liquid. EI Mass Spec: 146.0 MH+

**Example 12**

**4-But-2-ynyloxy-benzenesulfonyl chloride**

To a solution of 0.146g (1.0 mmol) of the product of Example 11 in 0.3 mL of dichloromethane in an acetone/ice bath under $N_2$ was dropwise added a solution of 0.073 mL (1.1 mmol) of chlorosulfonic acid in 0.3 mL of dichloromethane. After the addition was complete, the ice bath was removed and the reaction was stirred at room temperature for 2h. To the reaction was then dropwise added 0.113 mL (1.3 mmol) of oxalyl chloride, followed by 0.015 mL DMF. The reaction was heated to reflux for 2h and then diluted with hexane and poured into ice water. The organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo to provide 0.130mg (53%) of the desired product as a light brown solid.

**Example 13**

**(1R,2R)-2-({[4-(2- Butynyloxy)phenyl]sulfonyl}amino)-cyclohexanecarboxylic acid**

To a room temperature solution of 1.5g (10.2 mmol) of trans-2-amino-1-cyclohexylcarboxylic acid in 75 ml of dioxane:$H_2O$ (1:1) containing 2.55 ml (18.3 mmol) of triethylamine was added 3.0g (11.2 mmol) of 4-butynyloxybenzenesulfonyl chloride. The mixture was stirred at 25°C for 18 h. The resulting mixture was diluted with ethyl acetate and washed with 1N aqueous hydrochloric acid (3X). The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to

afford (1R,2R)-2-({[4-(2- butynyloxy)phenyl]sulfonyl}amino)cyclohexanecarboxylic acid as a white solid. Electrospray Mass Spec 352.2 $(M+H)^+$

**Example 14**

***tert*-Butyl (1R,2R)-2-({[4-(2- butynyloxy)phenyl]sulfonyl}amino)-cyclohexanecarboxylate**

To a solution of 2.1 g (6 mmol) of (1R,2R)-2-({[4-(2-butynyloxy)phenyl]-sulfonyl}amino) cyclohexanecarboxylic acid in 30 mL of toluene was added 6 mL (24 mmol) of N,N-dimethylformamide di-*tert*-butyl acetal. The resulting mixture was heated at 110°C for 4h under nitrogen and then allowed to cool to room temperature. The solution was then poured on top of a silica gel column. Chromatography on silica gel eluting with 10-20% ethyl acetate/hexane gave 1.7g of *tert*-butyl(1R,2R)-2-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)cyclohexane-carboxylate as a white solid. Electrospray Mass Spec 408.3 $(M+H)^+$

**Example 15**

***tert*-Butyl (1R,2R)-2-[{[4-(2- butynyloxy)phenyl]sulfonyl}(methyl)amino]-cyclohexanecarboxylate**

To a solution of 1.38 g (3.4 mmol) of *tert*-butyl (1R,2R)-2-({[4-(2- butynyl-oxy)phenyl]sulfonyl} amino) cyclohexanecarboxylate in 20 mL of DMF was added 0.164g (4.1 mmol) of 60% sodium hydride. The resulting mixture was stirred for 30 min at 25°C and then 0.26 mL (4.1 mmol) of iodomethane was added all at once. This reaction mixture was stirred for 0.5 hr at 25°C and then water and ethyl acetate were added. The organics were washed with water, dried over anhydrous potassium carbonate and concentrated in vacuo to provide *tert*-butyl (1R,2R)-2-[{[4-(2- butynyl-oxy)phenyl]sulfonyl}(methyl)amino] cyclohexanecarboxylate as a white solid. Electrospray Mass Spec 422.2 $(M+H)^+$

**Example 16**

**(1R,2R)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-cyclohexanecarboxylic acid**

To a solution of *tert*-butyl (1R,2R)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}-(methyl)amino]cyclohexanecarboxylate in 20 mL of dichloromethane was added 5 mL of trifluoroacetic acid and the mixture was stirred for 3h at room temperature. The solvent was then removed in vacuo and the residue was chromatographed on silica gel eluting with methanol/dichloromethane. Trituration with ethyl acetate/-

hexane provided 1.04 g of (1R,2R)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)-amino]cyclohexanecarboxylic acid as a white solid. Electrospray Mass Spec 364.3 $(M-H)^-$

**Example 17**

**(1R,2R)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxycyclohexanecarboxamide**

To oxalyl chloride (1.42 mL of a 2 M solution in dichloromethane) in dichloromethane at 0°C was added dimethylformamide (0.22 mL). After 15 min a solution of (1R,2R)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]cyclohexanecarboxylic acid in dimethylformamide was added and the resulting reaction mixture was stirred at room temperature for 1h.

In a separate flask, 3 mL of triethylamine was added to a 0°C mixture of 0.987 g of hydroxylamine hydrochloride in 7.6 mL of THF and 3.2 mL of water. After this mixture had been stirred for 15min at 0°C, the acid chloride solution was added to it in one portion and the resulting solution was allowed to warm to room temperature and stirred for another 18h. Ethyl acetate and aqueous sodium bicarbonate were then added to the reaction flask. The organic phase was washed with aqueous sodium bicarbonate and dried over anhydrous potassium carbonate. Concentration in vacuo and trituration with diethyl ether gave (1R, 2R)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]-N- hydroxycyclohexanecarboxamide as a white powder (485 mg). Electrospray Mass Spec 381.2 $(M+H)^+$

**Example 18**

**(1R, 2R)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide**

In the same manner as described in **Example 17**, 0.50 g (1.42 mmol) of (1R,2R)-2-({[4-(2- butynyloxy)phenyl]sulfonyl} amino) cyclohexanecarboxylic acid provided 0.32 g of (1R, 2R)-2-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide as a white solid. Electrospray Mass Spec 367.2 $(M+H)^+$.

**Example 19**

***tert*-Butyl 3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)propanoate**

To *tert*-butyl-2-aminopropanoate (2.0g, 11.0 mmol) in 20 mL of dichloromethane at 0°C was added triethylamine (6.75 mL, 48.4 mmol) followed by

4-(2-butynyloxy)phenylsulfonyl chloride (2.94 g, 12.1 mmol). An additional 10 mL of dichloromethane was added to the thick slurry. The mixture was stirred overnight then diluted with dichloromethane and washed sequentially with water, 2N aqueous citric acid and brine, then dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave a solid that was triturated with hexane/ethyl acetate to give *tert*-butyl 3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)propanoate (3.88 g) as an off-white solid, mp 63 – 65°C. Analysis for $C_{17}H_{23}NO_5S$: Calc'd: C, 57.77; H, 6.56; N, 3.96. Found: C, 57.68; H, 6.42; N, 3.90. Electrospray Mass Spec 354.2 $(M+H)^+$.

**Example 20**

**N-{[4-(2-Butynyloxy)phenyl]sulfonyl}-beta-alanine**

In the same manner as described in **Example 16** *tert*-butyl 3-({[4-(2-butynyloxy) phenyl]sulfonyl}amino) propanoate (1.0 g, 2.83 mmol) gave N-{[4-(2-butynyloxy)phenyl]sulfonyl}-beta-alanine (1.12 g) as a white solid. Electrospray Mass Spec 296.2 $(M-H)^-$.

**Example 21**

**3-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxypropanamide**

To N-{[4-(2-butynyloxy)phenyl]sulfonyl}-beta-alanine (0.80 g, 2.69 mmol) in dimethylformamide (5 mL) was added 1-hydroxybenzotriazole (0.436 g, 3.23 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.67 g, 3.5 mmol). After one hour 50% hydroxylamine in water (1.3 mL) was added. The reaction mixture was stirred overnight and concentrated in vacuo. Ethyl acetate was added and the organic phase washed with water (2X) and brine then dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave a white solid that was triturated with ethyl acetate to give 3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxypropanamide (0.30 g) as a white solid,. mp 118 – 128°C. Electrospray Mass Spec 313.3 $(M+H)^+$.

**Example 22**

***tert*-Butyl-3-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]propanoate**

To a solution of *tert*-butyl 3-({[4-(2-butynyloxy)phenyl]-sulfonyl}amino)-propanoate (1.0 g, 2.83 mmol) in dimethylformamide (5 mL) at 0°C was added sodium hydride (3.39 mmol) followed by iodomethane (211 uL, 3.39 mmol). After 72 hours the reaction mixture was diluted with ethyl acetate and washed with water and brine and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave *tert*-butyl-3-[{[4-(2-butynyloxy)phenyl]-sulfonyl}(methyl)amino]-propanoate (1.0 g) as a colorless oil. Electrospray Mass Spec 368.2 $(M+H)^+$.

**Example 23**

**N-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-methyl-beta-alanine**

In the same manner as described in **Example 16** *tert*-butyl-3-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]propanoate (0.863 g, 2.34 mmol) gave N-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-methyl-beta-alanine (0.760 g) as a white solid, mp 90-110°C. Electrospray Mass Spec 312.1 $(M+H)^+$.

**Example 24**

**3-({[4-(2-Butynyloxy)phenyl]sulfonyl} (methyl) amino)-N-hydroxypropanamide**

N-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-methyl-beta-alanine (0.7 g, 2.25 mmol) was converted to 3-({[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino)-N-hydroxypropanamide (0.525 g white solid) as described in **Example 21**. Analysis for $C_{14}H_{18}N_2O_5S$: Calc'd: C, 51.52; H, 5.56; N, 8.58. Found: C, 51.38; H, 5.16; N, 8.28. Electrospray Mass Spec 327.2 $(M+H)^+$.

**Example 25**

**(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}amino cyclopentanecarboxylic acid**

To a solution of cis-2-amino-1-cyclopentane (1.0 g, 7.74 mmol) in 1:1 water:dimethylformamide (10 mL) at 0°C was added sodium carbonate (2.7 g, 25.5 mmol) followed by 4-(2-butynyloxy)phenyl sulfonyl chloride (2.08 g, 8.5 mmol). The reaction mixture was allowed to warm to room temperature. After stirring overnight water and ethyl acetate were added and the mixture acidified to pH = 1 with 6N aqueous hydrochloric acid. The organic phase was washed with water and

brine and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave (1R, 2S)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino cyclopentanecarboxylic acid (1.58 g) as a white solid, mp 105–135°C. Electrospray Mass Spec 336.4 $(M+H)^+$.

**Example 26**

**(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclopentanecarboxamide**

(1R,2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}aminocyclopentane-carboxylic acid (0.506g, 1.5 mmol) was converted to (1R,2S)-2-[{[4-(2-butynyloxy)-phenyl]sulfonyl}amino)-N-hydroxycyclopentanecarboxamide (0.28 g) as described in **Example 21** to give an off-white solid (0.185 g), mp 140–145°C. Electrospray Mass Spec 353.4 $(M+H)^+$.

**Example 27**

***tert*-Butyl (1R, 2S)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino cyclopentanecarboxylate**

(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}amino cyclopentane-carboxylic acid (0.80 g) was converted to *tert*-butyl (1R, 2S)-2-[{[4-(2-butynyloxy)-phenyl]sulfonyl}amino cyclopentanecarboxylate as described in **Example 14** to give white crystals (0.60g), mp 97–100°C. Analysis for $C_{20}H_{27}NO_5$: Calc'd: C, 61.05; H, 6.92; N, 3.56. Found: C, 61.04; H, 6.79; N, 3.72. Electrospray Mass Spec 394.2 $(M+H)^+$.

**Example 28**

***tert*-Butyl (1R, 2S)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino cyclopentanecarboxylate**

*tert*-Butyl (1R, 2S)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}aminocyclo-pentanecarboxylate (0.50 g, 1.27 mmol) in dimethylformamide (4 mL) was treated with potassium carbonate (0.527g, 3.81 mmol) and iodomethane (95 uL, 1.53 mmol). After 18 hours the reaction mixture was concentrated in vacuo, diluted with ethyl acetate and washed with water and brine then dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave *tert*-butyl (1R, 2S)-2-[{[4-(2-butynyl-oxy)phenyl]sulfonyl} (methyl) amino cyclopentanecarboxylate as a white solid (0.495 g), mp 131–133°C. Electrospray Mass Spec 408.2 $(M+H)^+$.

**Example 29**

**(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl} (methyl) amino] cyclopentanecarboxylic acid**

*tert*-Butyl (1R, 2S)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino cyclopentanecarboxylate (0.44 g) was converted to (1R, 2S)-2-[{[4-(2-butynyloxy)-phenyl]sulfonyl}(methyl)amino]cyclopentanecarboxylic acid as described in **Example 16** to give a white solid (0.375 g). Electrospray Mass Spec 352.2 $(M+H)^+$.

**Example 30**

**(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl} (methyl) amino] N-hydroxycyclopentanecarboxamide**

(1R,2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino] cyclopentanecarboxylic acid (0.320 g) was converted to (1R,2S)-2-[{[4-(2-butynyloxy)phenyl]-sulfonyl}(methyl)amino]N-hydroxycyclopentanecarboxamide as described in **Example 21** to give white crystals (0.105 g), mp 160–164°C. Analysis for $C_{17}H_{22}N_2O_5S$: Calc'd: C, 55.72; H, 6.05; N, 7.64. Found: C, 55.40; H, 6.15; N, 7.50. Electrospray Mass Spec 367.25 $(M+H)^+$.

**Example 31**

**(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino cyclohexanecarboxylic acid**

Cis-2-amino-1-cyclohexane (1.2 g, 8.38 mmol) was converted to (cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino cyclohexanecarboxylic acid as described in **Example 25** to give a white solid (0.825 g), mp 172–175°C. Analysis for $C_{17}H_{21}NO_5S$: Calc'd: C, 58.10; H, 6.02; N, 3.99. Found: C, 58.32; H, 5.92; N, 3.87. Electrospray Mass Spec 350.1 $(M-H)^-$.

**Example 32**

**(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide**

(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}aminocyclohexanecarboxylic acid (0.300g, 0.854 mmol) was converted to (cis)-2-[{[4-(2-butynyloxy)phenyl]-sulfonyl}amino)-N-hydroxycyclohexanecarboxamide as described in **Example 21** to give an off-white foam (0.210 g). Electrospray Mass Spec 367.2 $(M+H)^+$.

**Example 33**

**(Cis)-*tert*-butyl-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino) cyclohexanecarboxylate**

(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}aminocyclohexanecarboxylic acid (0.38 g, 1.08 mmol) was converted to (cis)-*tert*-butyl-2-[{[4-(2-butynyloxy)-phenyl]sulfonyl}amino)cyclohexanecarboxylate as described in **Example 14** to give a white solid (0.450 g). Electrospray Mass Spec 408.2 $(M+H)^+$.

**Example 34**

**(Cis)-*tert*-butyl-2-[{[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino) cyclohexanecarboxylate**

(Cis)-*tert*-butyl-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino)cyclohexane-carboxylate (0.390 g, 0.956 mmol) was converted to (cis)-*tert*-butyl-2-[{[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino) cyclohexanecarboxylate as described in **Example 28** to give a colorless oil (0.260 g). Electrospray Mass Spec 422.2 $(M+H)^+$.

**Example 35**

**(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino) cyclohexanecarboxylic acid**

(Cis)-*tert*-butyl-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino)cyclo-hexanecarboxylate (0.220 g, 0.522 mmol) was converted to (cis)-2-[{[4-(2-butynyl-oxy)phenyl]sulfonyl}(methyl)amino)cyclohexanecarboxylic acid as described in **Example 16** to give a white solid (0.190 g). Electrospray Mass Spec 366.2 $(M+H)^+$.

**Example 36**

**(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino]-N-hydroxycyclohexanecarboxamide**

(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl) amino)cyclohexane-carboxylic acid (0.165 g, 0.45 mmol) was converted to (cis)-2-[{[4-(2-butynyloxy)-phenyl]sulfonyl} (methyl) amino]-N-hydroxycyclohexanecarboxamide as described in **Example 21** to give an off white solid (0.50 g). Electrospray Mass Spec 381.2 $(M+H)^+$.

**Example 37**

**(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)bicyclo [2.2.1] heptane-2-carboxylic acid**

3-Exo-aminobicyclo [2.2.1] heptane-2-exo carboxylic acid (1.0 g, 6.44 mmol) was converted to (1R, 2R, 3S, 4R)-(cis)-3-({[4-(2-butynyloxy)phenyl]-sulfonyl}-amino)bicyclo[2.2.1]heptane-2-carboxylic acid as described in **Example 25** to give a white solid (1.32 g), mp 195–215°C. Electrospray Mass Spec 364.3 $(M+H)^+$.

**Example 38**

**(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxybicyclo [2.2.1] heptane-2-carboxamide**

(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)bicyclo-[2.2.1]heptane-2-carboxylic acid (0.363 g, 1 mmol) was converted to (1R,2R,3S,4R)-(cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxybicyclo[2.2.1]heptane-2-carboxamide as described in **Example 21** to give a white solid (0.30 g). Analysis for $C_{18}H_{22}N_2O_5S$: Calc'd: C, 57.13; H, 5.86; N, 7.4. Found: C, 57.76; H, 6.12; N, 7.6. Electrospray Mass Spec 379.3 $(M+H)^+$.

**Example 39**

***tert*-Butyl (1R, 2R, 3S, 4R)-(cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)bicyclo [2.2.1] heptane-2-carboxylate**

(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)bicyclo-[2.2.1] heptane-2-carboxylic acid (0.80 g, 2.2 mmol) was converted to *tert*-butyl (1R,2R,3S,4R)-(cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)bicyclo[2.2.1]-heptane-2-carboxylate as described in **Example 14** to give a white solid (0.69 g), mp 94 – 99°C. Analysis for $C_{22}H_{29}NO_5S$: Calc'd: C, 62.98; H, 6.97; N, 3.34. Found: C, 62.65; H, 6.95; N, 3.7. Electrospray Mass Spec 420.3 $(M+H)^+$.

**Example 40**

***tert*-Butyl (1R, 2R, 3S, 4R)-(cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino)bicyclo [2.2.1] heptane-2-carboxylate**

*tert*-Butyl (1R, 2R, 3S, 4R)-(cis)-3-({[4-(2-butynyloxy)phenyl]-sulfonyl}-amino)bicyclo[2.2.1]heptane-2-carboxylate (0.55g, 1.31 mmol) was converted to *tert*-

butyl (1R, 2R, 3S, 4R)-(cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino)-bicyclo[2.2.1]heptane-2-carboxylate as described in **Example 28** to give a white solid (0.54 g), mp 120–125°C. Analysis for $C_{23}H_{31}NO_5S$: Calc'd: C, 63.72; H, 7.21; N, 3.23. Found: C, 63.34; H, 7.11; N, 3.55. Electrospray Mass Spec 434.2 $(M+H)^+$.

**Example 41**

**(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino)bicyclo [2.2.1] heptane-2-carboxylic acid**

*tert*-Butyl(1R,2R,3S,4R)-(cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}-(methyl)amino)bicyclo[2.2.1]heptane-2-carboxylate (0.45 g, 1.04 mmol) was converted to (1R,2R,3S,4R)-(cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)-amino)bicyclo [2.2.1] heptane-2-carboxylic acid as described in **Example 16** to give a white solid (0.37 g), mp 153–158°C. Analysis for $C_{19}H_{23}NO_5S$: Calc'd: C, 60.46; H, 6.14; N, 3.71. Found: C, 60.71; H, 5.94; N, 3.97. Electrospray Mass Spec 378.1 $(M+H)^+$.

**Example 42**

**(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino)-N-hydroxybicyclo [2.2.1] heptane-2-carboxamide**

(1R,2R,3S,4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}(methyl) amino)bicyclo-[2.2.1]heptane-2-carboxylic acid (0.30 g, 0.79 mmol) was converted to (1R, 2R, 3S, 4R)-(cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino)-N-hydroxybicyclo-[2.2.1]heptane-2-carboxamide (0.137 g) as described in **Example 21**. Electrospray Mass Spec 393.2 $(M+H)^+$.

Pharmacology

The ability of the compounds of the invention, or their pharmaceutically acceptable salts, to inhibit matrix metalloproteinases or TACE and, consequently, demonstrate their effectiveness for treating diseases modulated by matrix metalloproteinases or TACE is shown by the following in vitro assays.

Test Procedures for Measuring MMP-1, MMP-9, and MMP-13 Inhibition

These standard pharmacological test procedures are based on the cleavage of a thiopeptide substrates such as Ac-Pro-Leu-Gly(2-mercapto-4-methyl-pentanoyl)-Leu-Gly-OEt by the matrix metalloproteinases MMP-1, MMP-13 (collagenases) or MMP-

9 (gelatinase), which results in the release of a substrate product that reacts colorimetrically with DTNB (5,5'-dithiobis(2-nitro-benzoic acid)). The enzyme activity is measured by the rate of the color increase. The thiopeptide substrate is made up fresh as a 20 mM stock in 100% DMSO and the DTNB is dissolved in 100% DMSO as a 100 mM stock and stored in the dark at room temperature. Both the substrate and DTNB are diluted together to 1 mM with substrate buffer (50 mM HEPES pH 7.5, 5 mM $CaCl_2$) before use. The stock of enzyme is diluted with buffer (50 mM HEPES, pH 7.5, 5 mM $CaCl_2$, 0.02% Brij) to the desired final concentration. The buffer, enzyme, vehicle or inhibitor, and DTNB/substrate are added in this order to a 96 well plate (total reaction volume of 200 µl) and the increase in color is monitored spectrophotometrically for 5 minutes at 405 nm on a plate reader and the increase in color over time is plotted as a linear line.

Alternatively, a fluorescent peptide substrate is used. In this test procedure, the peptide substrate contains a fluorescent group and a quenching group. Upon cleavage of the substrate by an MMP, the fluorescence that is generated is quantitated on the fluorescence plate reader. The assay is run in HCBC assay buffer (50mM HEPES, pH 7.0, 5 mM $Ca^{+2}$, 0.02% Brij, 0.5% Cysteine), with human recombinant MMP-1, MMP-9, or MMP-13. The substrate is dissolved in methanol and stored frozen in 1 mM aliquots. For the assay, substrate and enzymes are diluted in HCBC buffer to the desired concentrations. Compounds are added to the 96 well plate containing enzyme and the reaction is started by the addition of substrate. The reaction is read (excitation 340 nm, emission 444 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line.

For either the thiopeptide or fluorescent peptide test procedures, the slope of the line is calculated and represents the reaction rate. The linearity of the reaction rate is confirmed ($r^2 > 0.85$). The mean ($x \pm sem$) of the control rate is calculated and compared for statistical significance ($p<0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generated using multiple doses of drug and $IC_{50}$ values with 95% CI are estimated using linear regression.

Test Procedure for Measuring TACE Inhibition

Using 96-well black microtiter plates, each well receives a solution composed of 10 µL TACE (final concentration 1µg/mL), 70µL Tris buffer, pH 7.4 containing 10% glycerol (final concentration 10 mM), and 10 µL of test compound solution in DMSO (final concentration 1µM, DMSO concentration <1%) and incubated for 10 minutes at room temperature. The reaction is initiated by addition of a fluorescent peptidyl substrate (final concentration 100 µM) to each well and then shaking on a shaker for 5 sec.

The reaction is read (excitation 340 nm, emission 420 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line. The slope of the line is calculated and represents the reaction rate.

The linearity of the reaction rate is confirmed ($r^2$ >0.85). The mean (x±sem) of the control rate is calculated and compared for statistical significance ($p<0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generate using multiple doses of drug and $IC_{50}$ values with 95% CI are estimated using linear regression.

Human Monocytic THP-1 Cell Differentiation Assay For Soluble Proteins (THP-1 Soluble Protein Assay)

Mitogenic stimulation of THP-1 cells cause differentiation into macrophage like cells with concomitant secretion of tumor necrosis factor (TNF-α and TNF receptor (TNF-R p75/80 and TNF-R p55/60) and Interleukin-8 (IL-8), among other proteins. In addition, non-stimulated THP-1 cells shed both the p75/80 and the p55/60 receptors over time. The release of membrane bound TNF-α and possibly TNF-R p75/80 and TNF-R p55/60, but not IL-8, is mediated by an enzyme called TNF-α converting enzyme or TACE. This assay can be used to demonstrate either an inhibitory or a stimulatory compound effect on this TACE enzyme and any cytotoxic consequence of such a compound.

THP-1 cells (from ATCC) are a human monocytic cell line which were obtained from the peripheral blood of a one year old male with acute monocytic leukemia. They can be grown in culture and differentiated into macrophage like cells by stimulation with mitogens.

For the assay, THP-1 cells are seeded from an ATCC stock which was previously grown and frozen back at 5 x 106/ml/vial. One vial is seeded into a T25-flask with 16 mls of RPMI-1640 with glutamax (Gibco) media containing 10 % fetal bovine serum, 100 units/ml penicillin, 100 µg/ml streptomycin, and 5 x $10^{-5}$ M 2-

mercapto-ethanol (THP-1 media). Each vial of cells are cultured for about two weeks prior to being used for an assay and then are used for only 4 to 6 weeks to screen compounds. Cells are subcultured on Mondays and Thursdays to a concentration of 1 x 105/ml.

To perform an assay, the THP-1 cells are co-incubated in a 24 well plate with 50 ml/well of a 24 mg/ml stock of Lipopolysacharide (LPS) (Calbiochem Lot# B13189) at 37¡C in 5% $CO_2$ at a concentration of 1.091 x $10^6$ cells/ml (1.1 ml/well) for a total of 24 hours. At the same time, 50 ml/well of drug, vehicle or THP-1 media is plated in appropriate wells to give a final volume of 1.2 ml/well. Standard and test compounds are dissolved in DMSO at a concentration of 36 mM and diluted from here to the appropriate concentrations in THP-1 media and added to the wells at the beginning of the incubation period to give final concentrations of 100 mM, 30 mM, 10 mM, 3 mM, 1 mM, 300 nM, and 100 nM. Cell exposure to DMSO was limited to 0.1 % final concentration. Positive control wells were included in the experiment which had mitogen added but no drug. Vehicle control wells were included as well, which were identical to the positive control wells, except that DMSO was added to give a final concentration of 0.083%. Negative control wells were included in the experiment which had vehicle but no mitogen or drug added to the cells. Compounds can be evaluated for their effect on basal (non-stimulated) shedding of the receptors by replacing the LPS with 50 ml/well of THP-1 media. Plates are placed into an incubator set at 5% CO2 and at 37° C. After 4 hours of incubation, 300 ml/well of tissue culture supernatant (TCS) is removed for use in an TNF-α ELISA. Following 24 hours of incubation, 700 ml/well of TCS is removed and used for analysis in TNF-R p75/80, TNF-R p55/60 and IL-8 ELISAs.

In addition, at the 24 hours timepoint, and the cells for each treatment group are collected by resuspension in 500 µl/well of THP-1 media and transferred into a FACS tube. Two ml/tube of a 0.5 mg/ml stock of propidium iodide (PI) (Boerhinger Mannheim cat. # 1348639) is added. The samples are run on a Becton Dickinson FaxCaliber FLOW cytometry machine and the amount of dye taken up by each cell is measured in the high red wavelength (FL3). Only cells with compromised membranes (dead or dying) can take up PI. The percent of live cells is calculated by the number of cells not stained with PI, divided by the total number of cells in the sample. The viability values calculated for the drug treated groups were compared to the viability value calculated for the vehicle treated mitogen stimulated group ("vehicle positive control") to determine the "percent change from control". This "percent change from control" value is an indicator of drug toxicity.

The quantity of soluble TNF-α, TNF-R p75/80 and TNF-R p55/60 and IL-8 in the TCS of the THP-1 cell cultures are obtained with commercially available ELISAs from R&D Systems, by extrapolation from a standard curve generated with kit standards. The number of cells that either take up or exclude PI are measured by the FLOW cytometry machine and visualized by histograms using commercially available Cytologic software for each treatment group including all controls.

Biological variability in the magnitude of the response of THP-1 cell cultures requires that experiments be compared on the basis of percent change from "vehicle positive control" for each drug concentration. Percent change in each soluble protein evaluated from the "vehicle positive control" was calculated for each compound concentration with the following formula:

$$\% \text{ Change} = \frac{\text{pg/ml (compound)} - \text{pg/ml (veh pos control)}}{\text{pg/ml (veh pos control)} - \text{pg/ml (veh neg control)}} \times 100$$

For the soluble protein (TNF-α, p75/80, p55/60, IL-8) studies under stimulated conditions, the mean pg/ml of duplicate wells were determined and the results expressed as percent change from "vehicle positive control". For the soluble protein (p75/80 and p55/60 receptors) studies under non-stimulated conditions, the mean pg/ml of duplicate wells were determined and the results expressed as percent change from "vehicle positive control" utilizing the following formula:

$$\% \text{ Change} = \frac{\text{pg/ml (compound neg control)} - \text{pg/ml (veh neg control}}{\text{pg/ml (veh neg control)}} \times 100$$

$IC_{50}$ values for each compound are calculated by non-linear regression analysis using customized software utilizing the JUMP statistical package.

For the cell viability studies, the viabilities (PI exclusion) of pooled duplicate wells were determined and the results expressed as % change from "vehicle positive control". The viability values calculated for the compound treated groups were compared to the viability value calculated for the "vehicle positive control" to determine "percent change from control" as below. This value "percent change from control" is an indicator of drug toxicity.

$$\% \text{ Change} = \frac{\text{\% live cells (compound)}}{\text{\% live cells (veh pos control)}} - 1 \quad X \ 100$$

References:

Bjornberg, F., Lantz, M., Olsson, I., and Gullberg, U. Mechanisms involved in the processing of the p55 and the p75 tumor necrosis factor (TNF) receptors to soluble receptor forms. Lymphokine Cytokine Res. 13:203-211, 1994.

Gatanaga, T., Hwang, C., Gatanaga, M., Cappuccini, F., Yamamoto, R., and Granger, G. The regulation of TNF mRNA synthesis, membrane expression, and release by PMA- and LPS-stimulated human monocytic THP-1 cells in vitro. Cellular Immun. 138:1-10, 1991.

Tsuchiya, S., Yamabe, M., Yamagughi, Y., Kobayashi, Y., Konno, T., and Tada, K. Establishment and characterization of a human acute monocytic leukemia cell line (THP-1). Int. J. Cancer. 26:1711-176, 1980.

Results of the above *in vitro* matrix metalloproteinase inhibition, TACE inhibition, and THP standard pharmacological test procedures are given in Table 1.

**Table 1:**

| Example # | MMP-1[a] | MMP-9[a] | MMP-13[a] | TACE[a] | THP[b] |
|---|---|---|---|---|---|
| 17 | >10 uM | >10 uM | >10 uM | 28 | 14 |
| 18 | >10 uM | >10 uM | >10 uM | 61 | 1 |
| 21 | >10 uM | >10 uM | >10 uM | 145 | 0 |
| 24 | >10 uM | ~10 uM | ~10 uM | 73 | 9 |
| 26 | >1 uM | 5056 | 672 | 15 | 23 |
| 30 | 2768 | 383 | 308 | 14 | 65 |
| 32 | >10 uM | ~10 uM | 1738 | 36 | 29 |
| 36 | 4229 | 1319 | 1820 | 53 | 23 |
| 38 | >10 uM | >10 uM | ~10 uM | 30 | 9 |
| 42 | ~10 uM | - | 1142 | 62 | 77 |

a) $IC_{50}$ (nM)

b) % Inhibition @ 3μM

Based on the standard pharmacological test procedures described above, the compounds of this invention are useful in the treatment of disorders such as arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, graft rejection, insulin resistance, bone disease and HIV infection.

The compounds of this invention are also useful in treating or inhibiting pathological changes mediated by matrix metalloproteinases such as atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis,

tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, infammatory bowel disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection.

Compounds of this invention may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such a solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferable sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

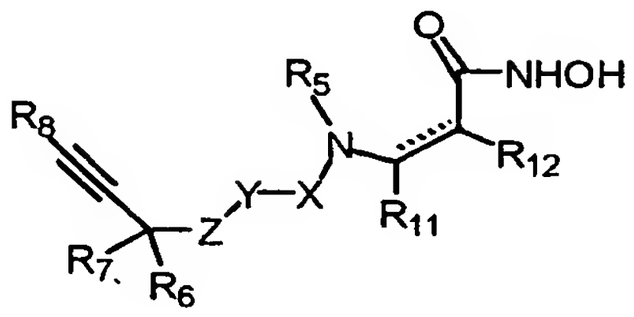
The compounds of this invention may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semi-solid emulsions of either the oil in water or water in oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage to be used in the treatment of a specific patient suffering a MMP or TACE dependent condition must be subjectively determined by the attending physician. The variables involved include the severity of the dysfunction, and the size, age, and response pattern of the patient. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated and standard medical principles.

Preferably the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

## CLAIMS

1. Hydroxamide acids of the formula:



B

where the C(=O)NHOH moiety and the $-NR_5-$ moiety are bonded to adjacent carbons;

wherein

X is $SO_2$ or $-P(O)R_{10}$;

Y is 5-10 membered heteroaryl ring having from 1-3 heteroatoms selected from N, $NR_9$, S and O, phenyl or naphthyl; with the proviso that X and Z may not be bonded to adjacent atoms of Y:

Z is O, NH, $CH_2$ or S;

$R_5$ is hydrogen or alkyl of 1-6 carbon atoms;

$R_6$ and $R_7$ are each, independently, hydrogen or methyl;

$R_8$ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, or phenyl;

$R_9$ is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or phenyl;

$R_{10}$ is alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, or 5-7 membered heteroaryl, having 1-3 heteroatoms selected from N, NR9, S and O;

$R_{11}$ and $R_{12}$ are, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, a 5-7 membered heteroaryl having 1-3 heteroatoms

selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, or phenyl, and the optional double bond represented by the dotted line is present; or

$R_{11}$ and $R_{12}$, together with the carbons to which they are attached, form a 5-10 membered saturated or unsaturated mono or bicyclic cycloalkyl optionally fused to one of a 5 to 7 membered saturated or unsaturated cycloalkyl ring, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, phenyl or napthyl rings; or

$R_{11}$ and $R_{12}$, together with the carbons to which they are attached form a 5-10 membered saturated or unsaturated mono- or bicyclic heterocycloalkyl having 1-2 heteroatoms selected from N, $NR_9$, S and O, optionally fused to one of a 5-7 membered mono or bi-cyclic heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered saturated or unsaturated cycloalkyl ring or a phenyl or napthyl ring;

the dotted line represents an optional double bond;

and n = 0-2; or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 wherein X is $SO_2$.

3. A compound according to Claim 1 or Claim 2 wherein Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively.

4. A compound according to any one of Claims 1 to 3 wherein Z is oxygen.

5. A compound according to any one of Claims 1 to 4 wherein $R_6$ and $R_7$ are hydrogen.

6. A compound according to any one of Claims 1 to 5 wherein $R_8$ is $-CH_2OH$ or methyl.

7. A compound according to Claim 1 which is selected from the group consisting of (1R,2R)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxycyclohexanecarboxamide;

(1R, 2R)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide;

3-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxypropanamide;

3-({[4-(2-Butynyloxy)phenyl]sulfonyl} (methyl) amino)-N-hydroxypropanamide;

(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclopentanecarboxamide;

(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl} (methyl) amino] N-hydroxycyclopentanecarboxamide;

(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide;

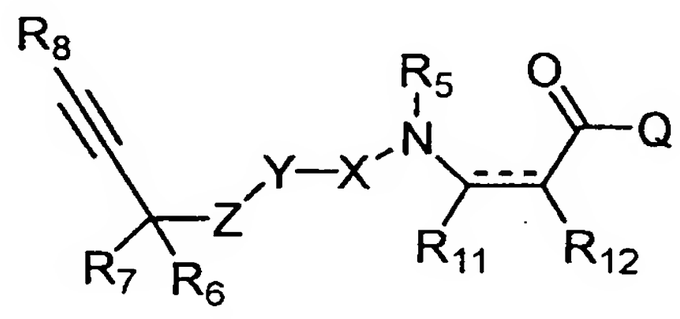
(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino]-N-hydroxycyclohexanecarboxamide;

(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxybicyclo [2.2.1] heptane-2-carboxamide; and

(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)-amino)-N-hydroxybicyclo [2.2.1] heptane-2-carboxamide.

8. A process for preparing a compound as claimed in Claim 1 which comprises one of the following:

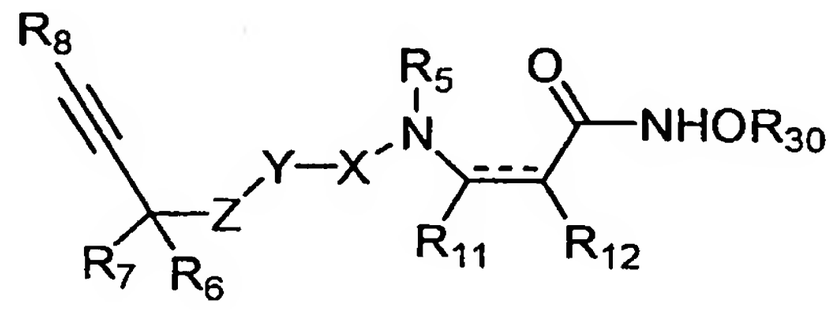
a) reacting a compound of formula V:



(V)

wherein $R_5$ $R_6$, $R_7$, $R_8$, and $R_{11}$ $R_{12}$, X, Y, Z and the dotted line are defined in Claim 1, and Q is OH or a reactive derivative thereof, with hydroxylamine to give a corresponding compound of formula **B**;

b) deprotecting a compound of formula VI:



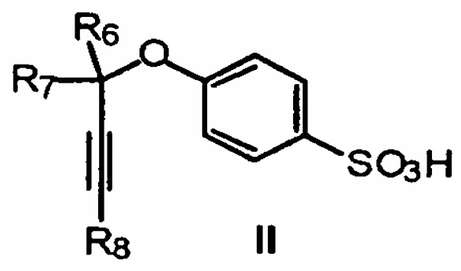

(VI)

wherein $R_5$ $R_6$, $R_7$, $R_8$, $R_{11}$ $R_{12}$, X, Y, Z and the dotted line are defined in Claim 1, and $R_{30}$ is a suitable protecting group, to give a corresponding compound of formula **B**

c) resolving a mixture (e.g. racemate) of optically active isomers of a compound of formula **B** to isolate one enantiomer or diastereomer substantially free of the other enantiomer or diastereomers;

d) acidifying a basic compound of formula **B** with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt.

9. A compound of the formula,

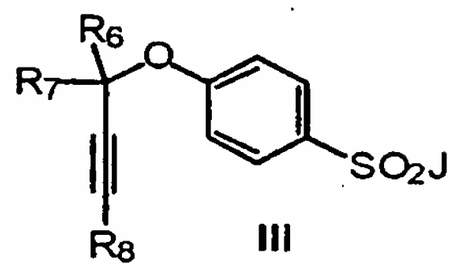



II

wherein $R_6$ and $R_7$ are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, -CCH;

and $R_8$ is alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, 5 to 10 membered heteroaryl having from 1 to 3 heteoatoms selected from N, $NR_9$, O or S, or 5 to 9 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, NR9, O or S.

10. A compound of the formula



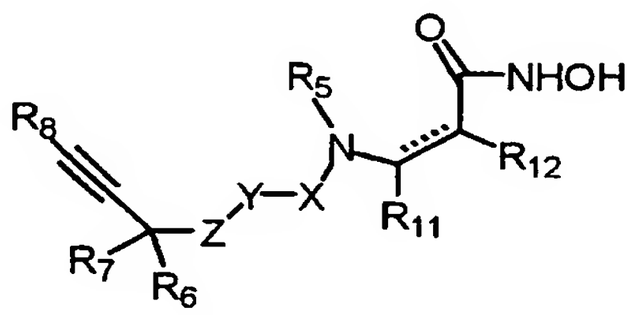
III

wherein $R_6$ and $R_7$ are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, -CCH;

$R_8$ is of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, 5 to 10 membered heteroaryl having from 1 to 3 heteoatoms selected from N, $NR_9$, O or S, or 5 to 9 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, O or S; and

J is fluorine, bromine, chlorine, 1,2,4-triazolyl, benzotriazolyl or imidazol-yl.

11. A method of inhibiting pathological changes mediated by TNF-α converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula:



B

where the C(=O)NHOH moiety and the $-NR_5-$ moiety are bonded to adjacent carbons;

wherein

X is $SO_2$ or $-P(O)R_{10}$;

Y is 5-10 membered heteroaryl ring having from 1-3 heteroatoms selected from N, $NR_9$, S and O, phenyl or naphthyl; with the proviso that X and Z may not be bonded to adjacent atoms of Y:

Z is O, NH, $CH_2$ or S;

$R_5$ is hydrogen or alkyl of 1-6 carbon atoms;

$R_6$ and $R_7$ are each, independently, hydrogen or methyl;

$R_8$ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, or phenyl;

$R_9$ is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or phenyl;

$R_{10}$ is alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, or L;

$R_{11}$ and $R_{12}$ are, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, or phenyl, and the optional double bond represented by the dotted line is present; or

$R_{11}$ and $R_{12}$, together with the carbons to which they are attached, form a 5-10 membered saturated or unsaturated mono or bicyclic cycloalkyl optionally fused to a 5 to 7 membered saturated or unsaturated cycloalkyl ring, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, phenyl or napthyl rings; or

$R_{11}$ and $R_{12}$, together with the carbons to which they are attached form a 5-10 membered saturated or unsaturated mono- or bicyclic heterocycloalkyl having 1-2 heteroatoms selected from N, $NR_9$, S and O, optionally fused to a 5-7 membered mono or bi-cyclic heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered saturated or unsaturated cycloalkyl ring or a phenyl or napthyl ring;

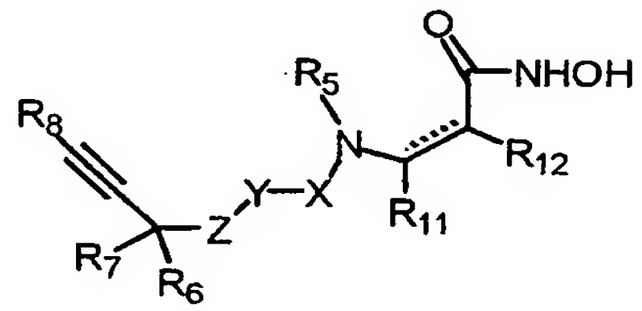
the dotted line represents an optional double bond;

and n = 0-2; or a pharmaceutically acceptable salt thereof.

12. The method according to Claim 11 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance,

septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.

13. A pharmaceutical composition comprising a compound having the formula:




**B**

where the C(=O)NHOH moiety and the $-NR_5-$ moiety are bonded to adjacent carbons;

wherein

X is $SO_2$ or $-P(O)R_{10}$;

Y is 5-10 membered heteroaryl ring having from 1-3 heteroatoms selected from N, $NR_9$, S and O, phenyl or naphthyl; with the proviso that X and Z may not be bonded to adjacent atoms of Y:

Z is O, NH, $CH_2$ or S;

$R_5$ is hydrogen or alkyl of 1-6 carbon atoms;

$R_6$ and $R_7$ are each, independently, hydrogen or methyl;

$R_8$ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, or phenyl;

$R_9$ is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or phenyl;

$R_{10}$ is alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, or L;

$R_{11}$ and $R_{12}$ are, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2

heteroatoms selected from N, $NR_9$, S and O, or phenyl, and the optional double bond represented by the dotted line, is present; or

$R_{11}$ and $R_{12}$, together with the carbons to which they are attached, form a 5-10 membered saturated or unsaturated mono or bicyclic cycloalkyl optionally fused to a 5 to 7 membered saturated or unsaturated cycloalkyl ring, a 5-7 membered heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, $NR_9$, S and O, phenyl or napthyl rings; or

$R_{11}$ and $R_{12}$, together with the carbons to which they are attached form a 5-10 membered saturated or unsaturated mono- or bicyclic heterocycloalkyl having 1-2 heteroatoms selected from N, $NR_9$, S and O, optionally fused to a 5-7 membered mono or bi-cyclic heteroaryl having 1-3 heteroatoms selected from N, $NR_9$, S and O, a 5-7 membered saturated or unsaturated cycloalkyl ring or a phenyl or napthyl ring;

the dotted line represents an optional double bond;

and n = 0-2; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

Inter...ional Application No
PCT/US 00/01865

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C311/29 C07F9/53 A61K31/18 A61K31/664 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 98 16503 A (AMERICAN CYANAMID CO) 23 April 1998 (1998-04-23) cited in the application claim 1 --- | 1-13 |
| A | US 5 514 716 A (GOWRAVARAM MADHUSUDHAN R ET AL) 7 May 1996 (1996-05-07) --- | 1-13 |
| A | WO 97 43245 A (DIXON BRIAN R ;BAYER AG (US); CHEN JINSHAN (US)) 20 November 1997 (1997-11-20) --- | 1-13 |
| P,X | WO 99 18076 A (AMERICAN CYANAMID CO) 15 April 1999 (1999-04-15) abstract --- | 1-13 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 9 May 2000 | ...06.00 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Janus, S |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Inter..ional Application No
PCT/US 00/01865

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | US 5 977 408 A (ZASK ARIE ET AL)<br>2 November 1999 (1999-11-02)<br>claim 1 | 1-13 |
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| X | & CHEMICAL ABSTRACTS, vol. 89, no. 21,<br>20 November 1978 (1978-11-20)<br>Columbus, Ohio, US;<br>abstract no. 179808,<br>ALLABERGENOV, K.D. ET AL.: "Corrosion inhibiting effect of acetylenic amino ethers of substituted phenols"<br>abstract | 9 |
| X | & IZV. VYSSH. UCHEBN. ZAVED., KHIM. KHIM. TECHNOL.,<br>vol. 21, no. 4, 1978, pages 478-480, | 9 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/01865

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11 and 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [X] Claims Nos.: 1, 2, 4-6, 8 and 10-13 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 00/01865

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims Nos.: 1, 2, 4-6, 8 and 10-13 (all in part)

Present claims 1, 2 4-6, 8 and 10-13 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In particular, attention is drawn to the "object of the invention" as defined by the applicant on p. 4, lines 8-13, where the scope of the application is clearly limited to only a part of present general formula B. Therefore, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds which do correspond to the conditions liste in the above-mentioned passage in the description, i.e. for the compounds of claim 3.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/01865

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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